16:53:16 OCA PAD AMENDMENT - PROJECT HEADER INFORMATION 11/25/96

Active

Project #: C-50-645 Cost share #: Rev #: 5
Center # : 10/24-6-R6368-6A0 Center shr #: OCA file #:
Work type : RES
Contract#: 2 R01 LM04692-06A1 Mod #: ADM. REVISION Document : GRANT
Prime #: Contract entity: GTRC

Subprojects ? : N CFDA: 93.879
Main project #: PE #:

Project unit: GVU Unit code: 02.010.314
Project director(s):
EZQUERRA N F COMPUTING (404)853-9173

Sponsor/division names: NIH-NATIONAL LIBRARY OF MED /
Sponsor/division codes: 108 / 009

Award period: 940201 to 970630 (performance) 970930 (reports)

Sponsor amount	New this change	Total to date
Contract value	0.00	691,990.00
Funded	0.00	691,990.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: KNOWLEDGE-BASED SYSTEM FOR CARDIAC IMAGE INTERPRETATION

PROJECT ADMINISTRATION DATA

OCA contact: Jacquelyn L. Bendall 894-4820

Sponsor technical contact	Sponsor issuing office
MR. PETER CLEPPER	MRS. SHELLY M. CAROW
(301)496-4221	(301)496-4195
NIH/NATIONAL LIBRARY OF MEDICINE	DHHS/PHS/NIH/NLM
BIOMEDICAL INFORMATION SUPPORT BRNCH	BIOMEDICAL INFORMATION SUPPORT BRNCH
9000 ROCKVILLE PIKE	9000 ROCKVILLE PIKE
BETHESDA, MD 20894	BETHESDA, MD 20894

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : NIH supplemental sheet
Equipment title vests with: Sponsor GIT X

Administrative comments -
ISSUED TO EXTEND PROJECT PERIOD TO 6-30-97 UNDER EXPANDED AUTHORITIES.

U
(4)

PROJECT CLOSEOUT - NOTICE

Closeout Notice Date 09-OCT-1997

Project Number C-50-645 Doch Id 38538

Center Number 10/24-6-R6368-6A0

Project Director EZQUERRA, NORBERTO

Project Unit GVU

Sponsor NIH-NATIONAL LIBRARY OF MED/

Division Id 3403

Contract Number 2 R01 LM04692-06A1 Contract Entity GTRC

Prime Contract Number

Title KNOWLEDGE-BASED SYSTEM FOR CARDIAC IMAGE INTERPRETATION

Effective Completion Date 30-JUN-1997 (Performance) 30-SEP-1997 (Reports)

Closeout Action:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	
Final Report of Inventions and/or Subcontracts	Y	
Government Property Inventory and Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

Comments

_

Distribution Required:

Project Director/Principal Investigator	Y
Research Administrative Network	Y
Accounting	Y
Research Security Department	N
Reports Coordinator	Y
Research Property Team	Y
Supply Services Department	Y
Georgia Tech Research Corporation	Y
Project File	Y

NOTE: Final Patent Questionnaire sent to PDPI

COMPLETE AND RETURN APPLICATION BY 1 DECEMBER 1994

SRC

Form approved through 6/30/94
OMB No. 0925-0001

50-645

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **APPLICATION FOR CONTINUATION GRANT**	REVIEW GROUP	TYPE 5	ACTIVITY R01	GRANT NUMBER LM04692-07
	TOTAL PROJECT PERIOD From: 02/01/94 Through: 01/31/97			
	REQUESTED BUDGET PERIOD From: 02/01/95 Through: 01/31/96			

To be verified by applicant. Check information in Items 1 through 6. If incorrect, furnish correct information in Item 13.

1. TITLE OF PROJECT

KNOWLEDGE-BASED SYSTEM FOR CARDIAC IMAGE INTERPRETATION

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Name and address, street, city, state, zip code)*

EZQUERRA, NORBERTO F
GEORGIA TECH RESEARCH CORP
GRAPHICS, VISUAL & USABILITY C
ATLANTA, GA 30332-0280

BITNET/INTERNET ADDRESS

2b. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT

2c. MAJOR SUBDIVISION

COLLEGE OF COMPUTING

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT *(See instructions)*

20 OTHER

4. APPLICANT ORGANIZATION *(Name and address, street, city, state, zip code)*

GEORGIA TECH RESEARCH CORP
GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GA 30332-0420

5. ENTITY IDENTIFICATION NUMBER

1580603146A1

6. TITLE AND ADDRESS OF ADMINISTRATIVE OFFICIAL

CONTRACTING OFFICER
OFFICE OF CONTRACT ADMIN
GEORGIA TECH RESEARCH CORP
ATLANTA, GA 30332-0420

BITNET/INTERNET ADDRESS

Complete the following *(see instructions)*

7. HUMAN SUBJECTS — 7a. NO [ ] YES [X] — If "YES" exemption no. or IRB approval date: 4 — 4b. Assurance of compliance no.:

8. VERTEBRATE ANIMALS — 8a. NO [XX] YES [ ] — If "YES," IACUC approval date: — 8b. Animal welfare assurance no.:

9. PERFORMANCE SITE(S) *(Organizations and addresses)*

1) GVU Center
College of Computing
Georgia Tech
Atlanta GA 30332-0280

2) Department of Radiology
Emory University
Clifton Road
Atlanta GA 30322

10. COSTS REQUESTED FOR NEXT BUDGET PERIOD

10a. DIRECT $ 188,580 10b. TOTAL $ 227,530

11. INVENTIONS AND PATENTS *(See instructions)*

[X] NO [ ] YES If "YES," [ ] Previously reported [ ] Not previously reported

TELEPHONE AND FAX INFORMATION

	AREA CODE	TELEPHONE NO. AND FAX NO.
12a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)*	404/	853-9173
	404/	853-0673
12b. NAME OF ADMINISTRATIVE OFFICIAL *(Item 6)* Janis L. Goddard	404	894-4817
	404	894-6956 (fax)
12c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 15)* Janis L. Goddard, Contracting Officer	404	894-4817
	404	894-6956 (fax)

BITNET/INTERNET ADDRESS

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBERS(S) WHERE ANSWERS APPLY.

	SIGNATURE	DATE
14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).	SIGNATURE OF PERSON NAMED IN 2a *(In ink. "Per" signature not acceptable.)*	11/28/94
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to cival penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).	SIGNATURE OF PERSON NAMED IN 12c *(In ink. "Per" signature not acceptable.)*	11/29/94

DETAILED BUDGET FOR NEXT BUDGET PERIOD DIRECT COSTS ONLY	FROM 2/1/95	THROUGH 1/31/96	GRANT NUMBER LM04692-07

PERSONNEL (*Applicant organization only*)		TYPE APPT. (*months*)	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED (*Omit cents*)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Norberto Ezquerra, PhD	P I	9	35.9	60,750	21,834	5,393	27,227
Norberto Ezquerra, PhD	P I	3	50	20,250	10,125	2,501	12,626
Steve Capell	Graduate Res.Asst.	12	50	GRA Stipend	15,204		15,204
Thomas Browne	Graduate Res Asst	12	50	GRA Stipend	15,204		15,204
Graduate Student	Graduate Res Asst	9	50	GRA Stipend	11,394		11,394
Chrissy Hendricks	Admin. Asst.	12	13.7	23,162	3,163	781	3,944
SUBTOTALS →					76,924	8,675	85,599

CONSULTANT COSTS	
EQUIPMENT (*Itemize*)	
SUPPLIES (*Itemize by category*) Publication Costs $1,000 Reproduction Costs 320 Computer Supplies 800 Film & film processing 378	2,498
TRAVEL Domestic: 1 trip for 2 individuals to Medical Informatics Conference	2,400
PATIENT CARE COSTS — INPATIENT	
PATIENT CARE COSTS — OUTPATIENT	
ALTERATIONS AND RENOVATIONS (*Itemize by category*)	
OTHER EXPENSES (*Itemize by category*) Computer software and hardware maintenance and College of Computing Networking, hardware and software support	6,879
SUBTOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD	97,376
CONSORTIUM/CONTRACTUAL COSTS Subcontract with Emory Univ Sch of Medicine DIRECT COSTS $ 58,092 INDIRECT COSTS $ 33,112 TOTAL →	91,204
TOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD (*Enter on Page 1, Item 10a*) →	$ 188,580

DETAILED BUDGET FOR NEXT BUDGET PERIOD DIRECT COSTS ONLY	FROM 2/1/95	THROUGH 1/31/96	GRANT NUMBER LM04692-07

PERSONNEL (*Applicant organization only*) NAME	ROLE ON PROJECT	TYPE APPT. (*months*)	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED (*Omit cents*) SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Ernest Garcia	PI	12	9%	125,000	11,250	2,813	14,063
E. Krawczynska	Co-Inv	12	20%	32,309	6,462	1,615	8,077
C.David Cooke	CompScien	12	30%	43,651	13,095	3,274	16,369
R. Folks	Res. Tech	12	20%	44,544	8,909	2,227	11,136
S. Clark	Biostatis	12	5%	40,768	2,038	510	2,548
SUBTOTALS →					41,754	10,439	52,193

CONSULTANT COSTS	
EQUIPMENT (*Itemize*)	
SUPPLIES (*Itemize by category*) Computer Supplies $249 Photographic Supplies $250	499
TRAVEL 1 trip/year for PI	800
PATIENT CARE COSTS — INPATIENT	
PATIENT CARE COSTS — OUTPATIENT	
ALTERATIONS AND RENOVATIONS (*Itemize by category*)	
OTHER EXPENSES (*Itemize by category*) Publication costs (reprints, color figs) $500 Partial Maintenance 4 Sun Sparc stations $4,100	4,600
SUBTOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD	58,092
CONSORTIUM/CONTRACTUAL COSTS - Subcontract budget for Emory Univ Sch of Medicine portion DIRECT COSTS $ 58,092 INDIRECT COSTS $ 33,112 **TOTAL** →	91,204
TOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD (*Enter on Page 1, Item 10a*) →	$ 188,580

BUDGET JUSTIFICATION	GRANT NUMBER LM04692-07

SUPPLEMENTAL INFORMATION REGARDING *ITEMS* IN THE PROPOSED BUDGET FOR THE NEXT PERIOD WHICH REQUIRE EXPLANATION OR JUSTIFICATION. *(See instructions)*

Norberto Ezquerra, Ph.D., will be the Principal Investigator for this research program. In this capacity, he will direct the technical aspects of all projects (1 through 6). His responsibilities also include supervision of graduate research assistants, coordinating activities with Emory University, and budgetary aspects of the program.

Steve Capell, B.S., will continue his research in this program by primarily focusing on Project 2. He is a graduate research assistant, and expects to pursue a career in a field related to this research.

Thomas Browne, B.S., has just begun to work on this research project. He will be a graduate research assistant focusing on Projects 3 and 4.

Graduate Research Assistant. This is a graduate student in the College of Computing not yet identified, who will serve as a graduate assistant and is expected to pursue the tasks of Project 5.

Chrissy Hendricks is an administrative support staff in the Graphics, Visualization and Usability Center in the College of Computing. She will support purchasing, financial record keeping, secretarial and clerical aspects of this project.

Supplies. It is expected that publications and conference presentations will result from this research, as in the past. The budget thus reflects expenses associated with journal publication and reprint costs ($1,000). The reproduction ($320), film and film processing costs ($378) to support this are shown. Computer supplies (paper, laser cartridges, tapes, etc.) are also shown in this item ($800).

Travel. The results of this research are going to be periodically presented at medical informatics conferences (e.g., SCAMC); two team members will attend each year to present various results.

Subcontract with Emory. The Radiology Department's human and material resources are an integral part of this research in terms of developing, implementing, and validating the methodology in the clinical setting. Additional justification for the subcontract appears in a subsequent page.

Other expenses. Computational resources represent an important part of medical informatics research. Although no funds are requested for equipment purchase, the costs of maintenance and upkeep of the computational resources dedicated to this project are shown in the budget. These include two types of expenses: those associated with computer equipment manufacturers' software and hardware maintenance, and those associated with the infrastructure and computer support in the College of Computing for networking hook-ups, communications support, and software installation. These considerations are directly related to all aspects of the research (Projects 1 through 6, especially 5, which is system integration and implementation in a networked environment). The total estimated for these costs is $6,879.

CURRENT BUDGET PERIOD	FROM 2/1/95	THROUGH 1/31/96

The following pertains to your CURRENT PHS budget. This information may be used in determining the amount of support for the NEXT budget period.

A. CURRENT BUDGET	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (1)	ESTIMATED UNOBLIGATED BALANCE (2)	EXPLAIN ANY SIGNIFICANT ESTIMATED UNOBLIGATED BALANCE IN COLUMN 2 (3)
TOTAL DIRECT COSTS	188,025	0	
INDIRECT COSTS *(As provided)*	36,588	0	
TOTALS ⟶	224,613	0	

Ernest V. Garcia, Ph.D. - is the Principal investigator of the Emory subcontract.

Dr. Garcia is a physicist with 18 years experience in the development of medical imaging algorithms particularly in nuclear cardiology. Dr. Garcia has been responsible for the development of computer methods for quantifying planar and tomographic myocardial perfusion studies which are currently in use in over 3,000 institutions world-wide. Dr. Garcia's role in this proposal is to give clinical and scientific guidance to the team, to assist in the design of algorithms, expert systems, and neural nets, and in all aspects of their validation. He will be responsible for the Emory budget and personnel. He is scheduled to be funded for 5% of his time.

Elzbieta Kravczynska, M.D., Ph.D. - is a co-investigator and an Associate in Radiology. She is a cardiologist with extensive clinical experience as well as experience in nuclear cardiology procedures. Her role will be to provide guidance to assure that all methodology developed is consistent with the clinical needs of nuclear cardiology. She will perform all data-base analysis, tabulation of results and also serve as an expert observer in interpreting patient studies. She is scheduled to be funded for 20% of her time.

C. David Cooke, MSEE - is a computer scientist and a Research Associate in Radiology. He is an Electrical Engineer with extensive experience in computer software and hardware. In particular he has developed an expertise in using the NExpert development environment. His role will be to develop software interfaces between medical imaging files and expert system, neural net and intelligent system's inputs. He will also implement many parts of the algorithms, heuristics, nets described for this project. He is scheduled to be funded for 30% of his time.

Russell Folks, R.T. - is a nuclear medicine research technologist with over 5 years experience in research methods. His role will be in the processing (for research purposes), analysis, and photographing and storing of all the patients' studies used to develop and validate the methods described in this proposal. He is scheduled to be funded for 20% of his time.

Supplies - Twelve reels of magnetic tape and one optical disk are requested to store the image files of the patients used for these developments. Two boxes of color printer paper and formatter film are requested as well as miscellaneous photographic and office supplies.

Travel - One trip per year is requested to present results from these investigations at clinical/technical meetings such as Computers in Cardiology, American Heart, Radiology Society of North America, SPIE, etc.

Other expenses -
Publication costs of $500 per year are requested to help defray the expense associated with publishing manuscripts with color prints necessary in reporting our work, for duplication and for reprints.

Computer cost - 50% of hardware and software service contract for the SUN IPX workstation ($1,500) used to develop algorithms, 50% service contract for PIXAR display system to optimally display results ($1,600), 50% of VAX 4000 used by the Emory team as a file server, network to imaging systems and for word processing (1,100). The remaining $ 938 are to defray service costs on the research GE 3000 STARCAM system used to process the patient studies.

OTHER SUPPORT *(Use continuation pages if necessary)*	GRANT NUMBER LM04692-07

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to significant delays in the review and/or funding of the application.

Other support is defined as all funds or resources, whether Federal, non-Federal, or institutional, available to the principal investigator/program director (and other key personnel named in the application) in direct support of their research endeavors through research or training grants, cooperative agreements, contracts, fellowships, gifts, prizes, and other means.

Reporting requirements are: For each of the key personnel, describe (1) all currently ***active*** support and (2) all applications and proposals ***pending*** review or award, whether related to this application or not. If the support is part of a larger project, identify the principal investigator/program director and provide the data for the relevant subproject(s). If an individual has no active or pending support, check "None." Use continuation pages as needed to provide the required information in the ***format*** as shown below. Key personnel are defined as all individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project.

Name Norberto Ezquerra Active X Pending ____ None ____

a. Source and identifying no. NHLBI HL 42052 P.I. E. Garcia

Title A Unified Approach to Quantify and Visualize Cardiac Imagery

b. Your role on project Co-Principal Investigator % Effort 15%

c. Dates and costs of entire project 12/1/88 - 12/31/96 $1,290,716 direct costs

d. Dates and costs of current year 1/1/95 - 12/31/95 $ 198,580 direct costs

e. Specific aims of project To quantify and visualize multi-dimensional data (coronary arterial structure and myocardial perfusion distribution)

f. Describe scientific and budgetary overlap None

g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.)

None

Name: Ernest V. Garcia, Ph.D. Active X

a. Source and identifying no. NHLBI HL42052 P.I. E. Garcia
Title A unified approach to quantify and visualize cardiac imagery
b. Role in Project Principal Investigator % Effort 15%
c. Dates and cost of entire project 12/01/88-12/31/96 -
$1,290,716 , direct costs
d. Dates and cost of current project 1/1/95 - 12/31/95-
$198,580 direct costs.
e. Specific aims of project To multidimensionally quantify, unify, and visualize the coronary arterial tree and the myocardial perfusion distribution.
f. Scientific and budgetary overlap - None

g. Describe adjustments if the present application is funded.
None, since this is this proposal.

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a. Source and identifying no. General Electric Co.
P.I. E. Garcia
Title Development of Computer Tools on GE systems
b. Role in Project Principal Investigator % Effort 5%
c. Dates and cost of entire project 4/93-3/95, $110,000
d. Dates and cost of current project 4/94-3/95, $50,000

e. Specific aims of project Implementation of software tools on GE systems for quantification of myocardial perfusion

f. Scientific and budgetary overlap. There is no overlap since these funds are to implement a commercial tool already developed rather than to perform any research.

g. Describe adjustments if the present application is funded.
None

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a. Source and identifying no. Toshiba Corporation of America.
P.I. E. Garcia
Title Development of Computer Tools on Toshiba systems
b. Role in Project Principal Investigator % Effort 5%
c. Dates and cost of entire project 6/94-5/95, $ 45,000
d. Dates and cost of current project 6/92-5/95, $ 90,000
e. Specific aims of project Implementation of software tools on Toshiba systems for quantification and display of myocardial perfusion

f. Scientific and budgetary overlap. There is no overlap since these funds are to implement a commercial tool already developed rather than to perform any research.

g. Describe adjustments if the present application is funded.
None

Name: C. David Cooke   Active X

a. Source and identifying no.   NHLBI HL42052   P.I. E. Garcia
Title A unified approach to quantify and visualize cardiac imagery
b. Role in Project   Principal Investigator   % Effort 6%
c. Dates and cost of entire project 12/01/88-12/31/96 -
$1,290,716 , direct costs
d. Dates and cost of current project 1/1/95 - 12/31/95-
$198,580 direct costs.
e. Specific aims of project To multidimensionally quantify, unify, and visualize the coronary arterial tree and the myocardial perfusion distribution.
f. Scientific and budgetary overlap - None

g. Describe adjustments if the present application is funded.
None, since this is this proposal.

a. Source and identifying no.   National Library of Medicine -
LM04692   P.I. Norberto Ezquerra, Ph.D.
Title Knowledge-Based System for Cardiac Image Interpretation
b. Role in Project   PI of subcontract   % Effort 30%
c. Dates and cost of entire project 11/93-10/96, $742,055 -
direct
d. Dates and cost of current project 2/94-1/95, $54,308 (direct, subcontract)
e. Specific aims of project To facilitate medical decision making through the integration of both basic and applied concepts of medical informatics.
f. Scientific and budgetary overlap This proposal
g. Describe adjustments if the present application is funded.
None

Name: Elzbieta Krawczynska   No other active support

Grant and Contract Support for: W. Scott Clark, Ph.D. as of November 18, 1994

(1) CURRENTLY ACTIVE SUPPORT

1. a) Epidemiology and Risk Factors Associated with HIV Infection in Infants Born to Seropositive Mothers in a Minority Population
   Cooperative Agreement No. U64CCU404456
   Centers for Disease Control
   Center for Infectious Diseases, Division of HIV/AIDS
   b) 25% effort
   c) May 1994 - April 1995
   d) $481,737
   e) Statistical and epidemiological evaluation of risk factors for mother-to-child HIV transmission
   f) overlap: none
   g) modifications: none

2. a) Georgia Comprehensive Sickle Cell Center
   NIH-90-HL-15-B
   Principal Investigator: James R. Eckman
   b) 20% effort
   c) April 1993-1998
   d) Year 1: $1,109,942 Year 2: $1,135,439 Year 3: $1,183,711
   Year 4: $1,225,897 Year 5: $1,244,012
   e) Development of a comprehensive sickle cell center in conjunction with Emory University, Grady Memorial Hospital, Georgia Institute of Technology, and the Sickle Cell Foundation
   f) overlap: none
   g) modification: none

3. a) Alzheimer's Disease Core Center
   NIA Grant P30AG10130
   Principal Investigator: Suzanne S. Mirra, M.D., overall PI
   b) 10% effort
   c) September 30 1991 - June 30 1996
   d) $3,235,680, direct costs, entire project
   e) This project provides for the establishment and funding of an NIA Alzheimer's Center at Emory University.
   f) none
   g) none

4. a) Knowledge-Based System for Cardiac Image Interpretation
   Principal Investigator: Ernest V. Garcia
   b) 5% effort
   c) December 1992 - November 1995
   d) Year 1: $58,644 Year 2: $59,832 Year 3: $62,646
   e) Development and comparison of an expert system for cardiac image interpretation
   f) overlap: none
   g) modifications: none

(2) PENDING SUPPORT

1. a) Etiology, Family Pattern and Cytogenetic Observations of Ovarian Cancer Among Chinese in Taiwan
   Principal Investigator: Fung-Chang Sung
   b) Biostatistical consultant
   c) 5 year period
   d) Consulting costs only: Year 1: $2,000 Year 2: $1,000 Year 5: $3,000
   e) To determine if Chinese women in Taiwan have risk factors for ovarian cancer similar to other oriental women and occidental women.
   f) overlap: none
   g) modification: none

2. a) Urinary Symptoms in Pregnancy: A Prospective Multi-Center Study to Analyze the Effects of Pregnancy on Lower Urinary Function
   Principal Investigator: L. Lewis Wall
   b) 10% effort
   c) October 1994 - September 1996
   d) Year 1: $144,198 Year 2: $135,581 Year 3: $79,848
   e) Enhance the understanding of the physiologic changes that take place in the lower urinary tract during normal pregnancy.
   f) overlap: none
   g) modifications: none

GRANT NUMBER
LM04692-07

PROGRESS REPORT SUMMARY

PRINCIPAL INVESTIGATOR
EZQUERRA, NORBERTO

APPLICANT ORGANIZATION	PERIOD OF THIS REPORT	
GEORGIA TECH RESEARCH CORPORATION	FROM	THROUGH
GEORGIA INSTITUTE OF TECHNOLOGY	02/01/94	01/31/95
ATLANTA, GA 30332-0420		

TITLE OF PROJECT
KNOWLEDGE-BASED SYSTEM FOR CARDIAC IMAGE INTERPRETATION

1. SPECIFIC AIMS

The overall objective of this research program is to develop a computer-based methodology to assist in the diagnosis of heart disease. More specifically, the goal is to develop, implement, and test a knowledge-based system to interpret both image and non-image information, placing the emphasis on single-photon emission tomographic (SPECT) perfusion imagery and other relevant, patient-specific information. The knowledge-based system, called PERFEX (for perfusion expert), combines methods of computer vision, artificial intelligence, computer graphics, and user-interface design to accomplish these objectives.

The aims of the proposed research are to significantly extend, refine, test, and validate PERFEX. There are six specific aims, as follows:

(1) To automatically determine the orientation of the left-ventricular (LV) myocardium. The aim is to employ computer vision and 3D graphics techniques to define the orientation of the LV and thus permit proper data "re-slicing" in a reliable, automated fashion.

(2) To modify, extend, and refine the knowledge base (KB). The aim is to extend the KB to include two perfusion agents, numerous clinical findings, and patient symptoms.

(3) To predict perfusion reversibility using artificial neural networks. The aim is to train a network to recognize and predict the information associated with reversible perfusion defects using artificial neural networks (ANNs), using the information associated with stress and myocardial thickening as inputs.

(4) To explore the interrelationships between symbolic and connectionist approaches. The aim is to utilize the connectionist structure of ANNs and extract symbolic information from them.

(5) To enhance and test overall system usability. The aim is to perform usability tests to both properly design a user interface and increase overall system acceptance and clinical utility.

(6) To statistically test and validate PERFEX. The aim is to conduct a number of studies designed by a statistician in order to rigorously and quantitatively evaluate the KB system.

Subsequently, these aims are discussed in the context of associated progress, methodologies used, technical problems, results, significance, and publications.

2. STUDIES AND RESULTS

Overall, the research program has progressed as planned in the original application. Some tasks appear to be on schedule (Aims 2 and 4), while some tasks are slightly ahead of schedule (e.g., Aims 1, 5 and 6), while one is slightly behind schedule (Aim 3). The work has resulted in two academic degrees for graduate students, six publications, two software disclosures, and several noteworthy clinical and scientific contributions.

(1) Automatic determination of the orientation of the left-ventricular (LV) myocardium.
Knowing the orientation of the LV mass is important, since diagnosis is based on examining the SPECT slices that are perpendicular to this orientation. The orientation axis had traditionally been defined manually (visually), by trained technologists. If the orientation axis is improperly selected, diagnostic results may be compromised; on the other hand, by defining the proper orientation axis, the data can be properly "re-sliced" perpendicularly to this axis. The aim of this task is to develop and validate a method to automatically determine this orientation (or pose) of the LV myocardial mass, and to compare the results of this method with those obtained by expert technologists.

This task has been completely finished, as explained in the next paragraph. The highlights of the results are the following: (a) a Ph.D. degree was awarded to Rakesh Mullick, the student who worked on this task with the PI (NE) serving as dissertation advisor; (b) numerous publications resulted from this work (see Section 7); and (c) the algorithm has already been ported to the platform of one company's (General Electric's) nuclear perfusion imaging scanner, and plans are underway to do similarly with other imaging companies.

The methodology has been fully developed, implemented and validated to automatically specify the orientation (or pose) of the LV from SPECT data. The axis can be determined either as a straight line or as a curve. The methodology involves numerous steps, including: (a) segmentation of the LV mass, using histogram analysis and model-based feature extraction; (b) image closure, to address the problem of SPECT slices that showed gaps in the LV structure; (c) determination of a polygonal surface fitted to the segmented, labelled LV mass; (d) topological goniometry, a novel technique to analyze the vectors normal to the interior polygons of the extracted surface, such that these vectors "point" toward the desired axis; and (e) extensive validation studies designed by, and conducted in collaboration with, a biostatistician (SC) using a set of 124 patient cases.

(2) To modify, extend, and refine the knowledge base
A knowledge base (KB) has been developed to interpret Thallium-201 (Tl) SPECT imagery and assist in the diagnostic decision-making process. The goal of this task is to (a) interpret Technicium 99-m SESTAMIBI (Tc) (as well as the Thallium imagery); (b) continue extending the KB to address more complex clinical cases, ; (c) enhance the robustness of the KB by considering information regarding myocardial thickening, hypertension, left bundle-branch block, renal transplant candidacy, electrocardiographic results, and patient symptoms. As explained subsequently, progress has been achieved as planned in the initial application, and no major technical problems or unexpected setbacks have been encountered.

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(b) and (c) Extensions and refinements to the KB: Several systematic studies have been conducted to identify and understand incorrect conclusions reached by PERFEX, and a categorization of these incorrect results has been made. Three major issues have been identified: (i) incorrect PERFEX conclusions due to incompleteness of the KB; (ii) problems in the organization and/or control of the KB; and (iii) other minor technical problems (such as improper datafile header information, etc.). All problems of type (ii) and (iii) have been corrected, and problems due to lack of robustness have been used to identify, prioritize, and begin correcting the KB. This latter issue represents an ongoing activity to be emphasized during the next project period. The modifications recently introduced to the KB has been initially verified with a small sample (less than 30) of patient cases; these verification studies confirm that the KB system is performing as designed. Over 100 patient cases have been identified and processed in order to use them for the various validation projects. Validation is expected to be conducted mainly during the next project period.

(3) To predict perfusion reversibility using artificial neural networks

Perfusion tests, such as Tl imaging, normally consist of imaging the patient during stress and at rest (the latter providing information regarding defect reversibility). However, the clinical test using Tc permits measuring the stress perfusion distribution as well as the rate of myocardial thickening, which is an additional indicator of myocardial viability and may obviate the need for the second (at-rest) test. By considering the stress and thickening information, the reversibility (at-rest) image information can be predicted. The goal is to train an artificial neural network (ANN) to correctly predict this information using stress and thickening information as input.

Data from 30 patient studies have been used for developing an ANN to predict reversibility characteristics, using stress perfusion and percent thickening as inputs. The dataset represents both healthy and abnormal cases.The stress perfusion and thickening information from each study is stored in 32 values (16 values each for each perfusion and percent thickening); each of the 16 values corresponds to a different myocardial region. The output of the ANN consists of 16 values associated with localized reversibility. A three-layer, backpropagation network with adaptive learning and momentum was used, varying the number of nodes in the internal (hidden) layers to maximize predictive power. We have encountered some difficulty with this task, primarily due to the lack of data: the size of the dataset relative to the network topology requires that the sample size be used for both training and testing using the N-1 approach (leaving one sample for testing and the rest for training, and going through all the permutations allowed by the dataset). While the training results have been encouraging, the errors associated with the testing results are deemed unacceptable. We are currently exploring several avenues: increasing the dataset size (which requires a labor-intensive clinical process, and we have had to wait for more studies to become available); reducing the complexity of the input and output configurations (from 16 to fewer values); introducing "network biases" that exploit a priori knowledge of regional myocardial relationships (and that can be represented in the ANN through specific node interconnections); and other training strategies.

(4) To explore the interrelationships between symbolic and connectionist approaches.

The connectionist approach, exemplified through ANNs (Aim 3, above), consists of constructing networks that learn through a training procedure. Once trained, these networks thus exhibit some sort of "knowledge" that is somehow contained in the connectionist structure itself. Symbolic approaches, by contrast, aim to represent knowledge explicitly, as in rule-based systems, for instance. The goal of this task is to extract symbolic knowledge from the connectionist approach, by considering a number of recent advances in connectionism that analyze the topology, weights, and connections in ANNs, and inferring certain types of symbolic knowledge. The result would be a hybrid, symbolic-connectionist system to interpret imagery. Since this task is serially dependent on Aim (3), this task will be initiated in the next project period, as originally planned.

(5) To enhance and test overall system usability
It is well known that numerous knowledge-based systems in medicine have suffered from lack of clinical utility despite proven accuracy and reliability, possibly because of difficulty of use and because systems are sometimes developed outside the clinical environment. The goal of this task is to insure that clinicians are involved in continually using and improving prototype versions of our system, and to conduct a series of formal usability tests that further enhance overall acceptance and use.

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(6) System testing and validation
The goal of this task is to design statistically sound tests to determine system accuracy and validity. This is not a separate task, but is rather integrated in each of the other (five) tasks. This task has been ongoing, and will continue throughout the project by employing a biostatistician (SC) to design, conduct, and interpret a number of retrospective and prospective studies as well as other statistical analyses. In year 3, this aim will include multi-center trials of the KB system.

The orientation-determination algorithm of Aim (1) has undergone extensive testing, as discussed in Section 2-(1) and shown in the accompanying SNM abstract. The KB validation (Aim 2) continues to undergo extensive testing, as discussed in Section 2-(2) and Section 4. The validation efforts associated with the other tasks (Aims 3 and 4) are underway and will be continued through the next project period. The usability testing (Aim 5) has been accomplished, as described in Section 2-(5).

3. SIGNIFICANCE

(1) Clinical significance

The results thus far achieved in various tasks have noteworthy clinical significance. The integration of other relevant, clinical information (beyond the information contained in the images) will give this knowledge-based system the capability of providing more comprehensive and robust decision-making support regarding the diagnosis of heart disease.

Since the system is capable of performing automatic processing of the information from acquisition through interpretative stages, an important reduction has been achieved in the number of steps that would normally be perfomed by humans. For instance, an algorithm that automatically determines the LV myocardial mass (Aim 1) results in a more robust, quicker, and more reliable method of data reslicing. This is the case since the intra- and inter-observer variabilities associated with the traditional manual approach are eliminated, and, in addition, the algorithmic approach also frees humans of this tedious task, resulting in a savings of time and resources that can be redirected toward other problems of the diagnostic process.

Extension of the KB to handle other imaging agents (Tl-201 as well as Tc-99m) gives the interpretation system more generality and clinical usefulness in terms of cardiac image interpretation. In addition, a general quantification program has been developed which is capable of quantifying any imaging agent. Furthermore, the use of a single clinical test (using Tc-99m SESTAMIBI) that measures both stress perfusion and percent myocardial thickening, represents a significant reduction in health care costs, patient risk, and patient discomfort.

The user-centered, human-computer interface also represents a clinically significant contribution. This is important for several reasons: on one hand, the clinical users have themselves served a direct and vital role in system design and development, and, on the other, the interface provides a mechanism to interact with the image data, the clinical report, and the system's conclusions in a manner that is intuitive, visual, and clinically meaningful.

(2) Scientific and academic significance

The LV orientation determination algorithm has been generalized to other problems, resulting in a methodology that can determine the pose or orientation of any object imbedded in a 3D dataset (other biomedical and metereological applications have been considered). Furthermore, the work in knowledge representation and reasoning has resulted in an approach that integrates visual, temporal, and uncertainty reasoning models. In addition, the efforts associated with artificial neural network construction leads to a method for incorporating both connectionist and symbolic approaches into a single system, yielding a model for hybrid knowledge-based processing.

As previously noted, a Ph.D. degree and M.S. thesis have resulted from this year's efforts. In addition to the concomitant academic documents (thesis and dissertation), a number of publications have likewise resulted from this project period, as outlined in Section 7.

4 PLANS FOR NEXT YEAR OF SUPPORT

In general, no major changes or modifications to the original plans are expected.

Aim 1: Automatic determination of the orientation of the left-ventricular (LV) myocardium. As previously pointed out, this task has been completed.

Aim 2: Modifications, extensions, and refinements of the knowledge base. The thrust will be placed on continuing the KB extensions already initiated (discussed in Section 2), and also on validation. Sixty-one (61) Tl-201 cases (with catheterization correlation) will be analyzed during the next project period to verify the extensions and modifications introduced to the KB. In addition, sixty (60) Tc-99m patient cases (30 with catheterization correlation and 30 without) will be used to verify PERFEX results with this imaging agent.

Aim 3: Prediction of perfusion reversibility using artificial neural networks. As discussed in Section 2, some difficulty has been encountered in constructing an ANN due to limited data availability. We are currently exploring, and will continue to explore, several avenues: increasing the dataset size (which requires a labor-intensive clinical process, and we have had to wait for more studies to become available); reducing the complexity of the input and output configurations (from 16 to fewer values); introducing "network biases" that exploit a priori knowledge of regional myocardial relationships (and that can be represented in the ANN through specific node interconnections).

Aim 4: Exploration of symbolic-connectionist approaches. Since this task is serially dependent on Aim (3), this task will start in the next project period, as originally planned.

Aim 5: Enhancements and testing of overall system usability. A major effort has already been conducted to design a human-computer interface that is intuitive and clinically useful. As further modifications and extensions are incorporated into the KB system, corresponding enhancements to this interface will be integrated as appropriate. The associated usability tests will likewise be conducted in order to achieve an iterative design.

Aim 6: Statistical testing and validation of PERFEX. This is an ongoing effort, as previously noted. Each task will undergo a number of associated testing and validation studies in collaboration with the project biostatistician (SC).

5 HUMAN SUBJECTS

Exemption #4: Research involving the collection and study of existing data and records.

6 VERTEBRATE ANIMALS

Not applicable.

7 PUBLICATIONS

1. "Automatic Orientation Determination of LV Short Axis from SPECT data." Ph.D. dissertation, R. Mullick, primary advisor N. Ezquerra; School of Electrical and Computer Engineering, June 1994.

2. "Clinical Evaluation of Automated Technique to Reorient Left-Ventricular Myocardium in Cardiac SPECT," R. Mullick, N. ezquerra, C.D. Cooke, R. Folks, and E. Garcia, <u>Journal of Nuclear Medicine</u>, Vol. 35, No. 5, 116P, Proc. of Society of Nuclear Medicine, June 1994.

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GRANT NUMBER
LM04692-07

PROGRESS REPORT SUMMARY

PRINCIPAL INVESTIGATOR
EZQUERRA, NORBERTO

APPLICANT ORGANIZATION	**PERIOD OF THIS REPORT**	
GEORGIA TECH RESEARCH CORPORATION	FROM	THROUGH
GEORGIA INSTITUTE OF TECHNOLOGY	02/01/94	01/31/95
ATLANTA, GA 30332-0420		

TITLE OF PROJECT
KNOWLEDGE-BASED SYSTEM FOR CARDIAC IMAGE INTERPRETATION

1. SPECIFIC AIMS

The overall objective of this research program is to develop a computer-based methodology to assist in the diagnosis of heart disease. More specifically, the goal is to develop, implement, and test a knowledge-based system to interpret both image and non-image information, placing the emphasis on single-photon emission tomographic (SPECT) perfusion imagery and other relevant, patient-specific information. The knowledge-based system, called PERFEX (for perfusion expert), combines methods of computer vision, artificial intelligence, computer graphics, and user-interface design to accomplish these objectives.

The aims of the proposed research are to significantly extend, refine, test, and validate PERFEX. There are six specific aims, as follows:

(1) To automatically determine the orientation of the left-ventricular (LV) myocardium. The aim is to employ computer vision and 3D graphics techniques to define the orientation of the LV and thus permit proper data "re-slicing" in a reliable, automated fashion.

(2) To modify, extend, and refine the knowledge base (KB). The aim is to extend the KB to include two perfusion agents, numerous clinical findings, and patient symptoms.

(3) To predict perfusion reversibility using artificial neural networks. The aim is to train a network to recognize and predict the information associated with reversible perfusion defects using artificial neural networks (ANNs), using the information associated with stress and myocardial thickening as inputs.

(4) To explore the interrelationships between symbolic and connectionist approaches. The aim is to utilize the connectionist structure of ANNs and extract symbolic information from them.

(5) To enhance and test overall system usability. The aim is to perform usability tests to both properly design a user interface and increase overall system acceptance and clinical utility.

(6) To statistically test and validate PERFEX. The aim is to conduct a number of studies designed by a statistician in order to rigorously and quantitatively evaluate the KB system.

Subsequently, these aims are discussed in the context of associated progress, methodologies used, technical problems, results, significance, and publications.

2. STUDIES AND RESULTS

Overall, the research program has progressed as planned in the original application. Some tasks appear to be on schedule (Aims 2 and 4), while some tasks are slightly ahead of schedule (e.g., Aims 1, 5 and 6), while one is slightly behind schedule (Aim 3). The work has resulted in two academic degrees for graduate students, six publications, two software disclosures, and several noteworthy clinical and scientific contributions.

(1) Automatic determination of the orientation of the left-ventricular (LV) myocardium.
Knowing the orientation of the LV mass is important, since diagnosis is based on examining the SPECT slices that are perpendicular to this orientation. The orientation axis had traditionally been defined manually (visually), by trained technologists. If the orientation axis is improperly selected, diagnostic results may be compromised; on the other hand, by defining the proper orientation axis, the data can be properly "re-sliced" perpendicularly to this axis. The aim of this task is to develop and validate a method to automatically determine this orientation (or pose) of the LV myocardial mass, and to compare the results of this method with those obtained by expert technologists.

This task has been completely finished, as explained in the next paragraph. The highlights of the results are the following: (a) a Ph.D. degree was awarded to Rakesh Mullick, the student who worked on this task with the PI (NE) serving as dissertation advisor; (b) numerous publications resulted from this work (see Section 7); and (c) the algorithm has already been ported to the platform of one company's (General Electric's) nuclear perfusion imaging scanner, and plans are underway to do similarly with other imaging companies.

The methodology has been fully developed, implemented and validated to automatically specify the orientation (or pose) of the LV from SPECT data. The axis can be determined either as a straight line or as a curve. The methodology involves numerous steps, including: (a) segmentation of the LV mass, using histogram analysis and model-based feature extraction; (b) image closure, to address the problem of SPECT slices that showed gaps in the LV structure; (c) determination of a polygonal surface fitted to the segmented, labelled LV mass; (d) topological goniometry, a novel technique to analyze the vectors normal to the interior polygons of the extracted surface, such that these vectors "point" toward the desired axis; and (e) extensive validation studies designed by, and conducted in collaboration with, a biostatistician (SC) using a set of 124 patient cases.

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A knowledge base (KB) has been developed to interpret Thallium-201 (Tl) SPECT imagery and assist in the diagnostic decision-making process. The goal of this task is to (a) interpret Technicium 99-m SESTAMIBI (Tc) (as well as the Thallium imagery); (b) continue extending the KB to address more complex clinical cases, ; (c) enhance the robustness of the KB by considering information regarding myocardial thickening, hypertension, left bundle-branch block, renal transplant candidacy, electrocardiographic results, and patient symptoms. As explained subsequently, progress has been achieved as planned in the initial application, and no major technical problems or unexpected setbacks have been encountered.

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The results thus far achieved in various tasks have noteworthy clinical significance. The integration of other relevant, clinical information (beyond the information contained in the images) will give this knowledge-based system the capability of providing more comprehensive and robust decision-making support regarding the diagnosis of heart disease.

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5 HUMAN SUBJECTS

Exemption #4: Research involving the collection and study of existing data and records.

6 VERTEBRATE ANIMALS

Not applicable.

7 PUBLICATIONS

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2. "Clinical Evaluation of Automated Technique to Reorient Left-Ventricular Myocardium in Cardiac SPECT," R. Mullick, N. ezquerra, C.D. Cooke, R. Folks, and E. Garcia, Journal of Nuclear Medicine, Vol. 35, No. 5, 116P, Proc. of Society of Nuclear Medicine, June 1994.

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PROGRESS REPORT *(Personnel and Study Subjects)*

GRANT NUMBER

LM04692-07

All Personnel for the Current Budget Period
and Any Planned Changes in Personnel for the Next Budget Period

Use two sections. In the first section list *All Current Personnel*. In the second section list *Planned Personnel Changes.*

Name	Degree(s)	SSN	Role on Project (*e.g., PI, Res. Assoc.*)	Date of Birth (*MM/DD/YY*)	Annual % Effort
Norberto Ezquerra	Ph.D.	267-92-9836	P I	02/21/49	36
Ernest V. Garcia	Ph.D.	261-90-5323	Co-PI (Emory)	09/14/48	9
Elzbieta Kravczynska	MD, Ph.D.	252-49-1413	CoInvestigator	01/28/38	20
C. David Cooke	M.S.	433-33-7940	CoInvestigator	08/05/63	30
Russell Folks	B.S.	223-82-1163	CoInvestigator	09/02/54	20
S. Clark	Ph.D.	265-06-5935	CoInvestigator	07/21/62	5

Provide the number of subjects enrolled in the study ***to date*** according to the following categories. (See Page 8 for definitions.)

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	TOTAL
Female							
Male							
Unknown							
TOTAL							

CHECKLIST

GRANT NUMBER

LM04692-07

Check the appropriate boxes and provide the information requested. Make this page the last page of the signed original of the applicatio

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made by checking the appropriate boxes and verified by the signature of the OFFICIAL SIGNING FOR APPLICANT ORGANIZATION on the FACE PAGE of the application. Descriptions of individual assurances/certifications begin o page 9 of Specific Instructions.

a. Human Subjects *(Complete Item 7 on the Face Page)*

☐ Full IRB Review ☐ Expedited Review

Use of Human Subjects ☐ Change ☐ No Change Since Previous Submission

b. Vertebrate Animals *(Complete Item 8 on the Face Page)*

Use of Vertebrate Animals ☐ Change ☐ No Change Since Previous Submission

c. Inventions and Patents *(Complete Item 11 on the Face Page)*

d. Debarment and Suspension ☐ No ☐ Yes *(Attach explanation)*

e. Lobbying

With Federal appropriated funds ☐ No

With other than Federal appropriated funds ☐ No ☐ Yes

(If "yes", see page 13, and attach Standard Form LLL, "Disclosure of Lobbying Activities," to the application behind the Checklist.)

f. Delinquent Federal Debt ☐ No ☐ Yes *(Attach explanation)*

g. Misconduct in Science (Form PHS 6315) ☐ Filed ☐ Not Filed

If filed, date of Initial Assurance or latest Annual Report ____________

h. Civil Rights	i. Handicapped Individuals	j. Sex Discrimination	k. Age Discrimination
Form HHS 441	Form HHS 641	Form HHS 639-A	Form HHS 680
☐ Filed	☐ Filed	☐ Filed	☐ Filed
☐ Not Filed	☐ Not Filed	☐ Not Filed	☐ Not Filed

2. PROGRAM INCOME *(See Instructions, Page 16)*

All applications must indicate (Yes or No) whether program income is anticipated during the period(s) for which grant support is requested. ☐ No ☐ Yes. If "Yes" use the format below to reflect the amount and source(s) of anticipated program income.

Budget Period	Anticipated Amount	Source(s)

3. INDIRECT COST

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. Indirect costs will not be paid on foreign grants, construction grants, grants to Federal organizations and grants to individuals, and usually not on conference grants. Follow any additional instructions provided for Research Career Development Awards, Institutional National Research Service Awards, and specialized grant applications.

☐ DHHS Agreement Dated: ____________ ☐ No Indirect Costs Requested

☐ No DHHS Agreement, but rates established with ____________ Date ________

CALCULATION*

Enter proposed budget period:

Amount of base $____________ × Rate applied ____________ % = Indirect costs $ ____________

Add to total direct costs from form page 2 and enter new total on Face Page, item 10b

*Check appropriate box(es):

☐ Salary and wage base ☐ Modified total direct costs base ☐ Other base (Attach explanation)

☐ Off-site, other special rate, or more than one rate involved *(Attach explanation)*

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PERFEX: An Expert System for Interpreting 3D Myocardial Perfusion

NORBERTO EZQUERRA AND RAKESH MULLICK

Georgia Institute of Technology, Atlanta, GA

C. DAVID COOKE, ELIZABETH G. KRAWCZYNSKA, AND ERNEST V. GARCIA,

Emory University, Atlanta, GA

Abstract—*Interpreting three-dimensional (3D) data is generally recognized as an ill-defined and information-intensive task. The task becomes increasingly difficult in the context of medical diagnostic imagery, wherein the visual information must be interpreted in conjunction with other, nonvisual information. A novel approach is presented to perform the interpretation of such multidimensional information, concentrating on a medically important application: the interpretation of 3D tomograms of myocardial perfusion distribution. The overall goal is to assist in the diagnosis of coronary artery disease. The approach employs knowledge-based methods to process and map the 3D visual information into symbolic representations, which are subsequently used to infer structure (anatomy) from function (physiology), as well as to interpret the temporal effects of perfusion redistribution, and assess the extent and severity of cardiovascular disease both quantitatively and qualitatively. The knowledge-based system presents the resulting diagnostic recommendations in both visual and textual forms in an interactive framework, thereby enhancing overall utility. This paper presents the methodology underlying this approach, including the implementation and testing of this system within an actual clinical environment.*

1. INTRODUCTION

ONE OF THE MOST difficult, important, and ill-defined tasks in medicine is that of interpreting images. It has been pointed out (Connors, Harlow, & Dwyer, 1982) that a radiologist can disagree with his or her own diagnosis (when presented with the same image) as much as 15% of the time. One reason for this is that standardized methodologies for interpreting images generally do not exist, and visual interpretation is thus subject to observer variability. In addition, the decision-making process becomes increasingly difficult since expertise plays a major role, which implies that consistency, reliability, and accuracy are highly dependent on domain knowledge. Furthermore, clinical problem solving typically requires integrating imagery with information from other sources, such as electrocardiographic results, symptoms, and other relevant patient-specific data. Further complexity is added by requiring that the visual information, which commonly appears in distorted or two-dimensional (2D) formats, be visualized and integrated mentally by the clinician into more meaningful forms. Hence, the task of interpreting and visualizing medical imagery can be viewed as an information-intensive process requiring significant medical knowledge and clinical expertise, utilizing diverse types of information that may be distorted, misleading, or possibly inexact.

With this in mind, a knowledge-based (KB) system has been developed to assist in the decision-making process by providing expert-based knowledge with which to process and interpret patient-specific information that is both image as well as not image based, while also providing an interactive and clinically useful environment. The approach underlying this system incorporates techniques to accomplish the following: (a) automatically extract features from the 3D imagery, (b) cast the extracted features in symbolic form for subsequent knowledge-based processing, (c) infer anatomical information (i.e., possible locations of arterial lesions) from physiological information (i.e., myocardial perfusion distribution), (d) reason about temporally-derived image information regarding possible

Requests for reprints should be sent to Norberto Ezquerra, Associate Professor, College of Computing, Georgia Institute of Technology, Atlanta, GA 30332.

perfusion redistribution, (e) integrate other types of nonimage, patient-specific information, (f) assess the extent and severity of coronary artery disease, (g) model uncertainty to accommodate inexactness at various levels, (h) assess the overall patient condition, and (i) present all the relevant diagnostic information in a medically meaningful, interactive manner.

This KB system (PERFEX, for perfusion expert) has been under development for several years. The current system design is significantly different from previous ones (DePuey, Garcia, & Ezquerra, 1989; Ezquerra & Garcia, 1989) in terms of knowledge-base robustness, temporal reasoning, clinical testing, and user interface. It should be pointed out, however, that from the beginning the system was designed to be integrated in an actual clinical setting. For this reason, emphasis is placed on automating certain aspect aspects of the decision-making process, while user interaction has been emphasized in those aspects of the process where the clinician should, and probably prefers to, become involved in the process. This has recently resulted in an interface that both facilitates and invites usage. Another recent and important modification has been in terms of the implementation environment, which provides for greater access and portability. This paper describes these aspects of PERFEX, as well the methods employed in its development, implementation, and testing. In Section 2, a discussion is provided of the tomographic acquisition procedure, including an explanation of the importance of this procedure in terms of health care, and the type of information that the procedure generates. Section 3 is devoted to the knowledge representation, reasoning, and inferencing mechanisms, including the feature extraction process from which symbolic representations are obtained, the handling of uncertainty, and the integration of image, nonimage, and temporal information. Section 4 is concerned with the implementation and testing of the system. Finally, Section 5 makes concluding remarks and summarizes some of the current research activities.

2. MYOCARDIAL 3D IMAGING: METHODS AND RATIONALE

In order to better understand the methods employed in interpreting and visualizing 3D imagery, it would be worthwhile to first define the objectives of the underlying research and formulate the problems to be solved. In the broadest of terms, the overall objective is to provide a clinically useful, computer-based system to assist in diagnosing heart disease. Patients who are at risk of having heart disease generally undergo a series of clinical tests, including a nuclear "scan" that is performed to determine how well blood is perfusing throughout the myocardium (heart muscle). This test gives a measure of the extent and severity of disease, particularly in the left ventricle. The specific test is a cardiovascular nuclear medicine tomographic perfusion study, which is routinely used in medical centers. More precisely, the intent of this nuclear study is to detect and localize infarction (diseased or dead muscle tissue) as well as ischemia (viable myocardium but at risk of infarction). The procedure involves injecting the patient with a radiopharmaceutical tagged to go to the heart, such that the emitted radioactivity can be imaged, and, in turn, the image gives the myocardial perfusion distribution information.

Tomographic perfusion imaging using thallium-201 (henceforth referred to as Tl) is a clinically useful, noninvasive technique used to perform these studies (DePasquate et al., 1988). Patients undergoing Tl perfusion imaging are exercised in a fasting state according to a multistage treadmill protocol. At peak exercise, 3.5 millicurie (mCi) of Tl are injected, with exercise continuing for an additional 60 seconds. After approximately five minutes, and again three to five hours later, images of the patient are acquired using a rotating large field-of-view camera. These images taken at different times constitute the stress and delay images, corresponding respectively, to perfusion distributions while the patient is undergoing exercise and while he/she is at rest. The stress image is useful in determining perfusion defects in general (and infarctions in particular), while the delayed images are useful in determining possible redistribution of perfusion (i.e., ischemia, where a defect found during stress "disappears" or reverses when the patient is at rest).

For a tomographic acquisition, 32 images are acquired over a 180 degree arc, for a preset time of 40 seconds per image acquisition. These images are corrected for field nonuniformity and misalignment of the mechanical center of rotation. Following these corrections, the images are filtered and backprojected to reconstruct 6 mm-thick transaxial tomograms that encompass the entire heart. Coordinate transformations are subsequently applied to the transaxial tomograms to generate oblique, long- and short-axis tomograms, parallel to the long and short axes of the left ventricular myocardium. Figure 1 shows the long- and short-axis slices displayed using a color table that maps those areas containing relatively high concentrations of radioactive tracer into brighter colors (e.g., yellow and gold), while those areas that contain relatively low tracer concentrations are mapped into darker colors (e.g., magenta and blue). For each tomographic cut or slice, a maximal-count circumferential profile is then generated. Each point of these profiles represents the maximum (radioactivity) counts per pixel along a radius that extends from the center of the left ventricle to the limit of the radius of search. The profile is constructed from the values along 40 equally spaced radii (i.e., every 9 degrees). This procedure is performed for each stress (patient undergoing exercise) and delayed (patient at rest) tomographic study. After all the circumferential

FIGURE 1. A series of tomographic slices representing 3D myocardial perfusion distribution.

profiles are extracted, they are then interpolated to represent 15 slices (myocardial "height") by 40 angular locations (myocardial "circumference"). These 15 × 40 matrices are then plotted in a 2D polar representation, as shown in Figure 2, where the myocardial apex corresponds to the center region and the myocardial base corresponds to the periphery of the polar map. A similar plot (now shown) is generated for the delayed image.

During a clinical study, images of each patient are compared with those of "normal" patients. For this comparison, normal limit profiles are generated using the mean and standard deviation established from pooled profiles of normal patients for each angular location and each depth in the tomographic study. For an individual patient, the stress and delayed profiles are compared with the corresponding, gender-matched normal profiles and, from these comparisons, 15 × 40 matrices are generated which quantitatively express the location and severity of abnormal regions. For the purposes of visual diagnostic interpretation, these 15 × 40 matrices are normally displayed as color-coded polar plots in two forms: as standard deviation maps, representing the deviation from normal limits, and as a "black-out" map, in which those regions that fall beyond normal limits (usually 2.5 standard deviations from normal) are blackened out, as illustrated in Figure 2 (the standard deviation image is not shown in this figure). Thus, in the black-out displays, perfusion defects appear as contiguous pixels that have been set to zero (blackened out), whereas in the standard deviation image, each pixel that is below the mean normal value is converted to the corresponding number of standard deviations below that mean. Visual inspection is thus possible, since the color in either standard deviation or black-out image gives a measure of the degree of abnormality, with black representing severely abnormal. Similarly, the reversibility (i.e., delayed or at rest) image can be visually analyzed to gauge the extent to which perfusion defects reversed after several hours: whereas in the black-out image, the black region correspond to hypoperfusion, a whitened (white-out) region in the reversibility map represents perfusion redistribution several hours after stress.

Through clinical experience, interpretation of this visual information becomes possible by recognizing the many different possible patterns in the images. Thus, clinical interpretation by humans involves understanding the meaning of these patterns in terms of several things: possible artifacts, the physiology of perfusion, and the relationship between these and possible ischemia, infarction, coronary vessel anatomy, other clinical data, and overall patient condition. The polar map shown in Figure 2 is illustrative of one of the more popular forms for performing diagnostic interpretation. Typically, expert clinicians view images such as those shown in Figures 1 and 2 to assess patient condition. It is evident from these images and the foregoing discussions that much work has been done on the quantification of myocardial perfusion, and that these efforts have provided clinicians with a better understanding of the significance of perfusion defects (DePuey et al., 1989), thereby facilitating the assessment of heart disease. However, the resulting body of knowledge does not easily lead to mechanisms for computerized decision support. One obvious challenge consists of capturing and representing domain knowledge, which includes both visual and temporal knowledge for interpreting images taken at different times. Also, clinically useful decision support would require the integration of additional information that can be either numeric or textual in nature. Furthermore, symbolic representations of data as well as knowledge should allow for inexactness. These considerations

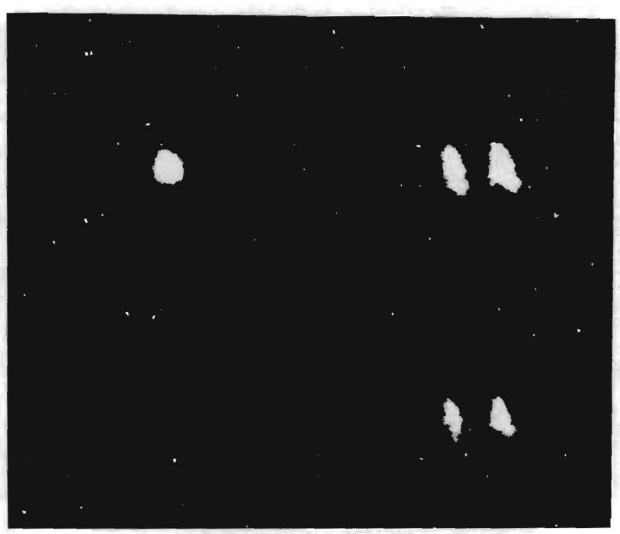

FIGURE 2. The 3D perfusion distribution in polar format.

present interesting knowledge engineering challenges and are the subject of the remainder of the paper.

3. KNOWLEDGE REPRESENTATION, REASONING, AND INFERENCING METHODS

A diagram representing the basic elements of PERFEX is shown in Figure 3 in terms of overall information flow. As shown in this figure, the input information consists of the image-derived information previously described (i.e., images corresponding to stress, standard deviation, and reversibility) as well as other patient-specific information. This section will describe how this information is used in PERFEX, and how the different components of PERFEX shown in Figure 3 relate to each other.

3.1. Symbolic Feature Extraction

The visual input to PERFEX consists of the standard deviation (*SD*), black-out (BO), and reversibility (RV) images described above. The information contained in these images represents the deviation from normal limits for a particular patient, where the black-out regions are those associated with severe hypoperfusion (usually beyond 2.5 standard deviations from normal limits). These images, then, actually represent the three-dimensional myocardial perfusion distribution in a quantitative form. Thus, the first task is that of mapping this visual information into symbolic form to infer diagnostic interpretations, essentially a vision task. For image processing purposes, grey-level intensity rather than color is used (since the color code is only intended to facilitate human visual inspection); the images are also cast in the form of 15 × 40 matrices (rather than in polar formats) without information loss. Initially, a search is conducted through the BO array for any pixel that has been set to zero (i.e., abnormal). This is followed by edge-hugging operations to isolate all other pixels set to zero that are also connected to the first 0-valued pixel found. This process identifies the first perfusion defect, and an entry is made in a list to keep record of this defect. In a systematic fashion, the entire BO array is searched to detect each and all perfusion defects, making the appropriate additions to the list. Upon termination of the search, information exists in a data file with the total number of defects and the location of each within the image. Once the defects have been detected and ordered in this fashion, a symbolic description is assigned to each defect. The description is defined spatially, in terms of regions of myocardial depth (basal, medial, proximal apical, and distal apical), and myocardial walls (septal, anterior, inferior, and lateral regions, as well as their pair-wise combinations). This scheme yields 32 possible regional descriptions (or descriptors for brevity) for localizing each perfusion defect, as shown in Figure 4. One defect can, of course, be composed of different descriptors. An example of a (small) defect with only one descriptor would be: "Antero-Septal-Medial," identifying a defect in the region at 11 o'clock. The localization of features in terms of descriptors is used for all three types of images used by PERFEX (BO, *SD*, and RV images).

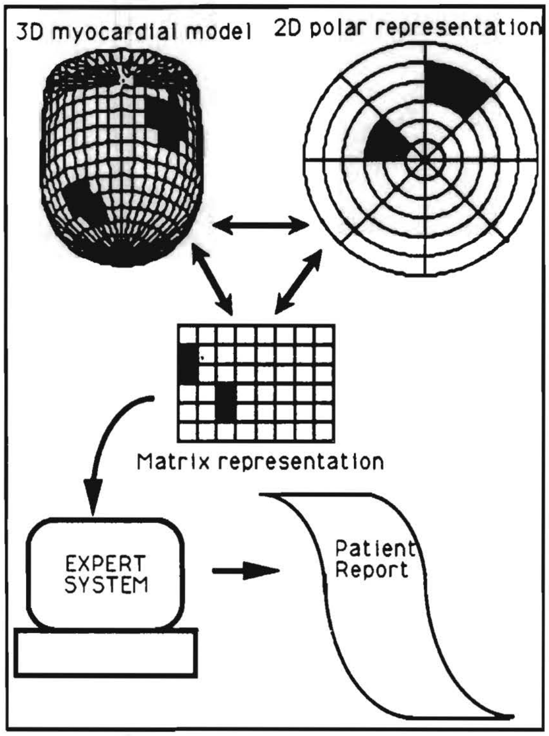

FIGURE 3. Overview of information flow in PERFEX.

3.2. Representation of Data Uncertainty and Defect Severity

To represent the severity of the perfusion defects, the standard deviation map was used. Each descriptor location in a defect (e.g., Antero-Septal_Medial) is associated with a descriptor in the *SD* map in a corresponding location. This *SD* descriptor has a numeric standard deviation value which, in fact, is a measure of severity. For the purpose of inferencing, as will be discussed later, this severity value can be expressed in terms of a certainty factor, obtained from an empirically-derived function that maps *SD* values to certainty factor values, the latter falling between -1 and $+1$ according to the Certainty Factor (CF) Model (Buchanan & Shortliffe, 1984). This provides a mechanism for representing evidence confirming (if the CF value is positive) or disconfirming (if the CF value is negative) the relative degree of abnormality associated with a descriptor (or groups of descriptors making up a defect), as well uncertain evidence (if the CF value is close to zero) of abnormality. The descriptors that have all its pixel values in the normal range are thus set to CF = -1.0, identifying them as definitely normally perfused regions; those having any of its pixel values in the ab-

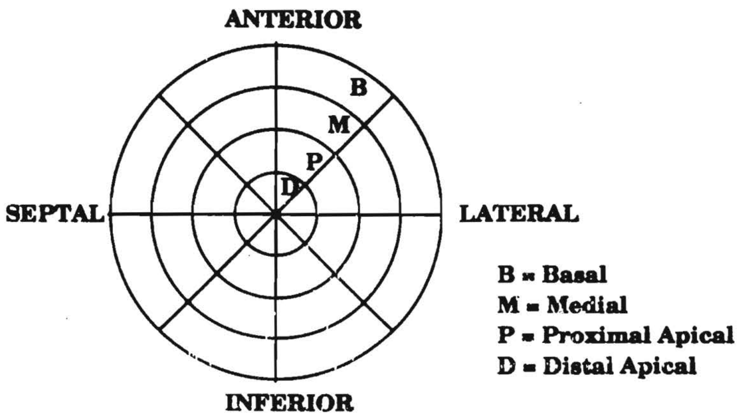

FIGURE 4. Diagram of the polar perfusion representation showing the 32 regions of interest and the corresponding set 32 symbolic descriptos.

normal range (2.5 standard deviations or more below the normal mean) are assigned according to the formula CF = 0.145SD −0.163, where *SD* is the average number of standard deviations below the mean normal response for pixels in the abnormal range.

A similar procedure is repeated for the descriptors associated with the delayed or RV images. The RV descriptor arrays are determined as the normalized difference between the delayed and stress T1-201 distributions. The reversibility array provides information as to whether a stress defect normalizes with time and is thus consistent with an ischemic event. These stress and reversibility descriptor files are used by the knowledge base for image interpretation.

This method of representing uncertainty, location, and severity with respect to stress and reversibility images was selected after much experimentation with different models of symbolic representation and inexact reasoning. The method is straightforward yet extremely powerful. Indeed, it is a symbolic mapping that is semantically meaningful, since the descriptors represent mutually distinguishable spatial regions with medically useful labels; the descriptors also cover the myocardial region of interest in sufficiently small segments while admitting evidence for or against disease for images taken at different times.

3.3. Knowledge Representation

The knowledge base of PERFEX is designed to relate the symbolic information just described, in conjunction with other, patient-specific data, to the presence (or absence) of coronary artery disease. The knowledge representation is achieved in terms of rules derived in a knowledge acquisition effort that spanned several years and involved careful analysis of several hundred actual clinical cases, conducted in collaboration with expert diagnosticians (Ezquerra & Garcia, 1989). Rule-based knowledge representation and acquisition are well known paradigms (Buchanan & Shortliffe, 1984; Musen, 1990), and although they remain active and important research areas, the present discussions will be primarily devoted to how these paradigms relate to PERFEX.

The knowledge base is organized in terms of knowledge islands, each of which contains knowledge about particular aspects of the overall interpretive process. Figure 5 is an illustration of the organization of the

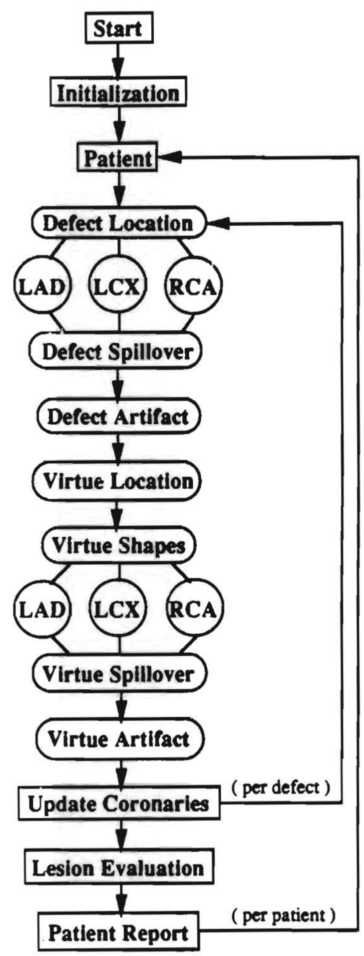

FIGURE 5. Knowledge structure of PERFEX in terms of knowledge islands.

knowledge base in terms of these knowledge islands. This figure also gives an indication of the hierarchy implicit in this organization structure and of the direction of flow of information. Since the knowledge structure is intimately connected with the inferencing mechanism, it may be worthwhile to describe both in a dynamic fashion, illustrated by means of a hypothetical consultation session.

The interpretive process begins by first considering patient-specific (nonimage) information. The information that is first considered includes the patient's age, sex, symptoms, and electrocardiographic results. These are used to obtain an estimate of the pretest likelihood of disease (i.e., the a priori probability of disease; (Diamond & Forrester, 1989). (Sex and age information may also be used by other rules during a consultation.) This pretest likelihood is calculated deterministically, and is used in overall patient evaluation. Referring to Figure 5 once again, one of the initial interpretive tasks deals with the characterization of the image information in terms of size and location of perfusion defects. This is accomplished by using the symbolic descriptors and their corresponding CF values. An illustration of how rules use these descriptor values is:

RULE ILM LOCATION

```
IF       Defect_Descriptor  IS ILM"
THEN     Defect_Location    IS "Infero_lateral_medial"
AND_DO   Nothing_Now
```

FIGURE 6. Sample rule for assigning symbolic descriptions to myocardial regions of interest.

This example (Fig. 6) illustrates the fact that the rules are constructed in both declarative and procedural manner. In the example, the symbolic descriptor (ILM) led to the conclusion or declaration of the location of the perfusion defect (inferolateral region; see Figure 4), while at the same indicated what action or procedure should be undertaken at this point (nothing at the moment). Thus, the rules contain premise, conclusion, and action clauses.

At present, over 300 rules are contained in the knowledge base. The rules contain expert-based knowledge and reasoning strategies representing the diagnostic process. Following the structure illustrated in Figure 5, this knowledge is structured in terms of knowledge islands to perform the following interpretive tasks: (a) characterize the image information sym ically in terms of location, size, and shape of st perfusion defects (as in the previous rule example); relate this symbolic information to evidence that c firms (or disconfirms) disease in three major vess the left anterior descending (LAD), left circum (LCX), and right coronary artery (RCA); (c) recogr shapes that, although suggestive of multiple-vessel ease because the defects "spill" over several territo are actually associated with only one vessel; (d) ognize the presence of artifacts (i.e., determine whe a defect is actual or a result of such effects as impro tomographic slice selection, attenuation, etc.); (e) de and localize regions of reversibility (the "opposite" perfusion defects, denoted as "virtues" in Fig. 5); relate this temporally derived information regard reversibility to specific arterial vessels (LAD, LCX, RCA); (g) recognize "spillover" shapes associated w perfusion redistribution (i.e., reversibility); (h) rec nize the presence of reversibility artifacts; (i) keep tr of how multiple defects affect each of the three ma coronary arteries of interest (LAD, LCX, and RC (j) suggest an overall diagnostic evaluation of the tient; and (k) provide a report that conforms to standard format of the report that is routinely u clinically. Another illustration of the type of knowle representation used in these knowledge islands is gi below.

Note that this is an example of a rule that consid sectors (rather than descriptors); these sectors repres larger myocardial regions and the symbolic repres tation in terms of sectors is built up from the descript using rules similar to that shown in Figure 6. In dition, the rule given in Figure 7 is an example of c that disconfirms evidence of disease in the right co nary artery (hence, the negative certainty factor va at the lower right); this will be expanded on later.

3.4. Representation of Temporal Reasoning

As previously mentioned, stress perfusion defects m indicate the presence of disease. However, the de image information can suggest that some or all of th perfusion defects are reversed at a later time, when patient is at rest. Thus, the information associated w reversibility, which is captured in terms of 32 symb descriptors analogous to the stress descriptors, rep

RULE LAD-DEFECT-NOT-RCA

```
IF     Defect_Sector      IS      Septo_Inferior AND Septo_Anterior
AND    Diseased_Coronary  IS      Right_Coronary_Artery
AND    Defect_Sector      IS_NOT  Infero_Lateral
THEN   Diseased_Coronary  IS      Right_Coronary_Artery (CF = -0.9)
DO     Decrease Right_Coronary_Artery_Evidence
```

FIGURE 7. A sample rule containing certainty factors and procedural clauses.

sents temporally defined information that modifies the conclusions that may have been inferred by PERFEX regarding possible disease, particularly regarding ischemia versus infarction. Thus, a temporal representation is necessary to account for these effects. It has been previously suggested that a full solution to the problem of time representation is an NP-hard issue, and requires certain compromises (Rucker, Maron, & Shortliffe, 1990). Although several logics of temporal inference exist (Allen, 1984; Fagan, 1980; Kahn, 1985), we have opted to follow a scheme similar to Rucker et al.'s (1990) of reducing complexity by using only specific time query representations, while adhering to the constraints associated with rule-based representation (Rucker et al., 1990). In our case, there is only one temporal phase of interest (associated with resting perfusion), thereby significantly reducing complexity. Thus, we employ a high-level representation of time in a two-phase procedure, corresponding to stress and delayed information. This scheme also resembles the reference intervals suggested by Allen (1984) and the contexts of Kahn et al. (1985). Therefore, the knowledge associated with reversibility is used as to modify inferences drawn from the stress imagery, where both phases are represented in an object-oriented framework. It should be added that most other applications involve multiple phases or segments of time, and that in those instances additional revision mechanisms may be necessary. In our case, however, the temporal representation is minimal (i.e., only two temporal segments need to be considered), and the revision mechanism occurs at a very high level to simply determine whether a particular defect is likely to be a "fixed" or "reversible" defect.

3.5. Inferencing and Uncertainty Reasoning

At this point, it is important to remark about the inferencing mechanism. During a typical consultation, PERFEX conducts a heuristic search that is primarily inductive in nature. As such, the inferencing is conducted in a forward chaning mode: from initial data to hypotheses (although it is possible to proceed in the reverse fashion). This is done primarily to incorporate the temporally based knowledge previously described. However, individual knowledge islands may be governed by locally deductive, goal-driven inferencing mechanisms.

As mentioned earlier, we have considered several models of reasoning with uncertainty in our research, including fuzzy set representation, probabilistic and qualitative reasoning, and belief networks (Sombe, 1990). However, it has been our experience that if the diagnostic accuracy obtained from different models are consistent with each other (in terms of sensitivity and specificity), then clinical utility will probably be decided by factors other than mathematical rigor (such as ease of use). With this in mind, we have selected those models that combine sufficient mathematical rigor with ease of implementation. At present, most of the uncertainty reasoning in PERFEX is based on the Certainty Factor Model, which is well known and has a number of well documented strengths and weaknesses (Buchanan & Shortliffe, 1984). In fact, it is precisely because of the wealth of knowledge that is available regarding the CF Model that it still remains in wide usage.

As stated earlier, the CF Model is used to express the relative certainty associated with the initial data, such as the severity of perfusion defects. In addition, this model is also used throughout the knowledge base. Thus, CF values are associated with the clauses in rules. The earlier sample rules, given in a simpler form for simplicity, more closely resemble the following form:

RULE ILM LOCATION

IF	Defect_Descriptor	IS	"ILM" (CF-ILM = 0.80)
THEN	Defect_Location	IS	"Infero_lateral_medial" (CF-LOC = 1.0)
AND_DO		Nothing_Now	

FIGURE 8. A sample rule containing certainty factors.

In general, if the CF value of the premise of a rule is greater than 0.2, the rule can be fired. The CF values are propagated according to the algorithms developed in the CF Model (Buchanan & Shortliffe, 1984). In keeping with the model, the combinatorics allow for providing relative measures of belief as the inferencing proceeds toward the goals, which in our case are the hypotheses concerning the presence of disease in each of three coronary vessels, and an evaluation of overall patient condition, as suggested in Figure 5.

4. SYSTEM IMPLEMENTATION, TESTING, AND RESULTS

A number of expert system shells have also been investigated throughout out research, including Intellicorp's KEE™, Texas Instrument's Personal Consultant™, IBM's ESDE™, and our own shell. At present, PERFEX is implemented in an object-oriented environment using Neuron Data's Nexpert Object™. This object-oriented framework provides some advantages, including inheritance properties and C-code. This software, however, has been extensively modified to incorporate the CF Model (which is intimately linked to inferencing) and to allow for a dynamic user interface.

The interface consists of a screen that displays a patient report, as shown in Figures 9 and 10. Figure 9 shows the screen as it might appear during a consultation session, displaying the polar plots at the bottom portion of the screen and the patient report at the top portion. The interface allows the user to point (with a mouse) and click on any of the fields in the report for further exploration and justifications. A full patient report is also printed, shown in Figure 10. Although the report seems somewhat visually intricate, it contains all the pertinent clinical information that is normally associated with the report filled out manually by the clinician. Thus, the screen serves as a report-generation mechanism as well. In the actual consultation, the screen shows the original imagery as well as portions of this report which can be scrolled up or down. The interaction is by means of a mouse, such that the user can click a field within the report, and initiate the process of asking the system to justify the reasoning behind the results or conclusions shown in the selected field. At present, we are developing this interface to support X-windows and to also show additional explanatory text and annotations. The reason why this interaction paradigm is useful is that the traditional way of conducting a clinical study is by having the clinician sit at a workstation to visually interpret the imagery, and PERFEX is designed to be a (transparent) part of the workstation environment.

A number of tests of PERFEX have been conducted or are underway. A preliminary pilot study consisting of a set of 20 patients has been conducted, comparing

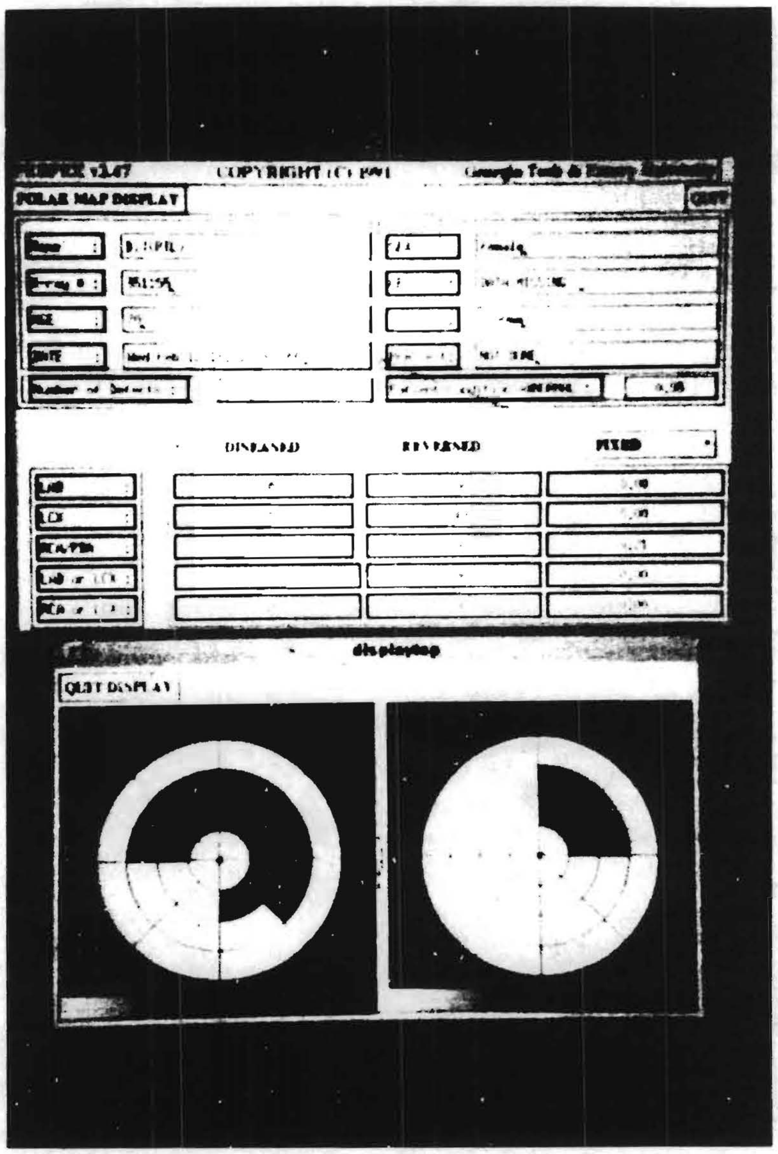

FIGURE 9. PERFEX user interface, showing the polar distribution (lower portion of screen) and patient report (upper portion of screen). Patient report can be accessed through a mouse-based, point-and-click paradigm.

PERFEX v.2.48	COPYRIGHT (C) 1991	Georgia Tech & Emory University

NAME	: C,K(STL)	SEX :	male
X-ray #	: 222582	CP :	DATA MISSING
AGE	: 52	ST :	0.00mm
DATE	: Wed Feb 12 15:06:25 1992	Pre-Test :	NOT DONE
Number of defects:	1	Patient Condition ABNORMAL:	0.95

	DISEASED	REVERSED	FIXED
LAD	0.95		0.54
LCX	0.70		0.54
RCA/PDA	0.86		0.54
LAD or LCX			
RCA or LCX			

NO DEFECT ARTIFACT FOUND

NO REVERSIBLE ARTIFACT FOUND

	#1	#2	#3	#4
DEFECT SHAPE				
standard	0.70			

NO REVERSIBLE SHAPE FOUND

SECTORS	DEFECT DESCRIPTION				REVERSIBILITY DESCRIPTION			
	#1	#2	#3	#4	#1	#2	#3	#4
LA	0.27				-0.63			
AL	0.62				-0.63			
LI	0.36				-0.63			
IL	0.87				-0.63			
APICAL	0.95				-0.63			
IS	0.76				-0.63			
SI	0.50				-0.63			
SA	0.48				-0.63			
AS	0.56				-0.63			
(D/V)IXELS	18				0			

FIGURE 10. Patient report produced by PERFEX. This is a hardcopy, full version of the report accessible through the user interface, shown in Figure 9.

the interpretations made by PERFEX with those of a human expert in thallium image interpretation. The human expert interpreted that, of the 20 patients, 3 were normal, 16 were consistent with coronary artery disease (CAD), and that one exhibited a count reduction in the anterior wall due to breast attenuation but was also probably normal (i.e., an artifact). PERFEX agreed with all of these interpretations, including identification of the breast artifact, although it called the patient probably abnormal. Of the 16 patients with evidence of CAD, PERFEX agreed with the expert in 7 out of 8 patients with ischemia, and in all 8 patients with infarction (and no ischemia). In addition, all of the 28 vascular territories (LAD, LCX, or RCA) identified by the human expert were correctly localized by PERFEX, although the latter incorrectly identified an additional 10 abnormal vascular territories. Of the 28 abnormal vascular territories, PERFEX correctly classified 12 of 16 as reversible (ischemic) and 11 of 12 as fixed (infarcted or scarred). These results agree very favorably with experts' interpretations of the images. The other significant consideration is that the results require less than 30 seconds to be generated by PERFEX upon receiving the image information, and that the knowledge-based system resides directly embedded in the actual clinical environment. At present, an extensive study of 100 patients is underway, and multicenter trials are planned.

5. CONCLUSIONS AND FUTURE DIRECTIONS

A knowledge-based approach to interpreting 3D tomographic myocardial perfusion distributions has been described. The approach is intended to suggest diagnostic recommendations regarding coronary artery disease. The methodology underlying this approach uses a rule-based paradigm to represent visual as well as temporal reasoning, and integrates patient-specific (nonimage) information to provide more comprehensive diagnostic decision support. The approach provides a novel mechanism for mapping visual information into symbolic representations that allow for knowledge-based processing. Another innovative feature consists of inferring structural information (associated with coronary vessel anatomy) from physiological function (representing myocardial perfusion). The methodology can serve as a model for interpreting 3D image information in general, and other types of medical images in particular.

The approach has been implemented in an object-oriented framework which allows for user interaction to query the system about specific conclusions and recommendations. The implementation system, PERFEX (for perfusion expert) is presently undergoing a number of clinical tests to determine accuracy, reliability, robustness, and overall clinical utility. Preliminary results indicate that the diagnostic interpretations made by PERFEX are highly consistent with those made by human experts, and that several factors in its design enhance clinical utility, including a significant degree of automation coupled with the possibility of user interaction.

At present, plans are underway to extensively test and evaluate PERFEX. A 100 patient study has been completed, and the results are currently being analyzed. In addition, ways to implement the system in different nuclear imaging systems are being investigated, and multicenter testing is being planned. Another significant direction of research concerns the aggregation of knowledge regarding other types of relevant clinical information. Furthermore, efforts are underway to develop methods to visualize in three dimensions the tomographic information, thus facilitating the overall diagnostic process. It is envisioned that these current efforts will lead to a comprehensive way to interpret and visualize cardiovascular anatomy and function.

Acknowledgement—This work was supported in part by Grant R29 LM04692 from the National Library of Medicine.

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A SUPPLEMENT TO

The Journal of Nuclear Medicine

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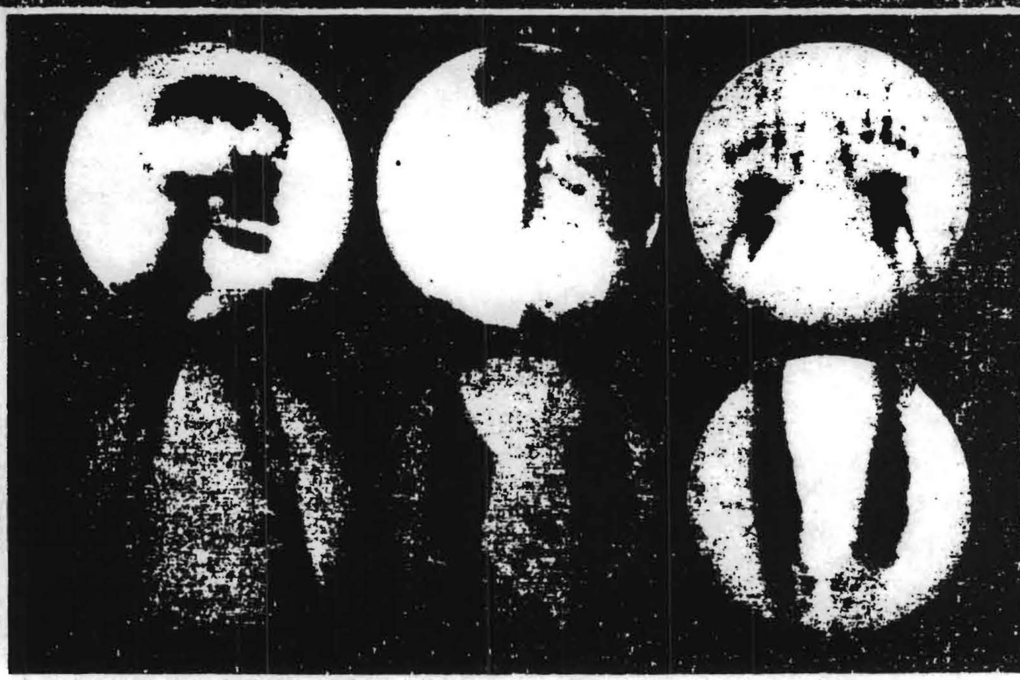
Volume 35, Number 5 • May 1994

ABSTRACT BOOK

Proceedings of the 41st Annual Meeting
Orlando, Florida, June 5–8



Technetium-99m-MDP images of a 55 yr-old woman with recurrent breast carcinoma demonstrate marked GM-CSF effects. Widespread symmetrical juxta-articular intense activity and marked frontoparietal activity in the calvarium are seen. Abstract 353.

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by a 2-compartment model, in which K1 was related to blood flow and extraction fraction.

	rest (R)	stress (S)	S/R
K1 (ml/g/min)	0.80±0.19	2.05±0.68	2.68±1.07
washout (/min)	0.10±0.01	0.15±0.02	1.49±0.33

Changes in blood flow in response to adenosine can be measured by compartmental analysis as well as washout analysis. However, mean stress/rest (S/R) ratios were almost 2 times higher (p=0.0048) for K1 estimates than for washout rates. Thus, quantitatively measuring CFR is feasible with fast dynamic SPECT and compartmental analysis of Tc-99m teboroxime kinetics. Further clinical investigations are required to define the diagnostic performance of this analysis method for the detection and quantification of coronary artery disease.

No. 462

AUTOMATIC ANALYSIS OF GATED MYOCARDIAL SPECT: DEVELOPMENT AND INITIAL VALIDATION OF A METHOD.

G.Germano, P.B.Kavanagh, H.Kiat, T.Chua, D.S.Berman, Cedars-Sinai Medical Center, L. A., CA.

We have developed a program which analyses 3-D image volumes from 8-,16- or 32-interval gated 99mTc myocardial SPECT studies, automatically segmenting the left ventricle (LV), calculating global and regional LV volumes, myocardial motion and myocardial thickening throughout the cardiac cycle, and deriving global and regional ejection fraction (EF) and stroke volume information. Segmentation of the LV is a multi-step process. An initial estimate for the center of the LV is found by searching for the peak of the cross-correlation between the 3-D image volume and a series of hollow spherical kernels. A group of radial profiles originating from that center point are then generated and yield an initial estimate for the position and orientation of the LV's long axis. The estimate is iteratively improved through the generation of count profiles perpendicular to the long axis, from which the position of the apex and the position and orientation of the valve plane are computed. All results are presented to the operator for verification and, if needed, interactive modification. The endo-, epi- and mid-myocardial surfaces of the LV are extracted for each frame in the cardiac cycle through the fitting of a gaussian distribution to the count profiles generated using a hybrid spherical/cylindrical coordinate system based on the geometry defined in the previous step. Surface discontinuities representing perfusion defects, identified by sub-threshold profiles, are iteratively filled using smoothness, the isocontours of the coordinate system and the geometry of the defect boundaries as constraints. The resulting surface, volume, and count data are used to automatically identify the end-systolic and end-diastolic image volumes, to generate regional and global wall motion and perfusion information and to estimate stroke volume and ejection fraction. These data are stored and can be analyzed with respect to a normal database. Validation of program-determined values for global LVEFs was performed against rest first pass (n=47) and equilibrium blood pool scintigraphy (n=21). The program ran successfully without operator modification in all patients with linear correlations for LVEF of 0.92 and 0.93, respectively (p<0.001). We conclude that our automated method correlates highly with conventional radionuclide measurements. Its use may allow quantitation of gated myocardial SPECT studies on a routine clinical basis, potentially facilitating diffusion of the technique.

No. 463

CLINICAL EVALUATION OF AUTOMATED TECHNIQUE TO REORIENT LEFT-VENTRICULAR MYOCARDIUM IN CARDIAC SPECT.

R Mullick and NF Ezquerra, Georgia Institute of Technology, and CD Cooke, RD Folks, and EV Garcia, Emory University School of Medicine, Atlanta, Georgia.

Clinical diagnostic interpretation of cardiac SPECT data requires reorientation of transaxial slices of the left ventricle (LV) into oblique (short, vertical and horizontal) slices. In order to generate these oblique slices manual and semi-automatic techniques have been used in the past to reorient the volume data set. These techniques are subjective, cumbersome and time-consuming. An automatic approach to determine the orientation (pose) of the LV and to delineate the long-axis has been developed. The developed methodology is composed of three main steps: (i) Segmentation - automatic identification of voxels corresponding to the LV; (ii) Topological Model Creation - Using the segmented data to generate a 3D polygonal representation of the LV structure; and (iii) Topological Goniometry - Geometric and graphical analysis of the topology to determine LV long axis. In this report, we present a clinical evaluation of this methodology. This approach was applied to 124 consecutive Tc-99m (50) and Tl-201 (74) cardiac SPECT datasets to automatically determine the LV orientation. The orientation of the LV was defined using the horizontal (α) and vertical (β) angles. The angles reported by the automatic approach were then compared to those manually determined by experts for use in the clinical evaluation. The results of our analysis is tabulated below:

Angle	Mean Absolute Deviation (degrees) Technetium-99m	Thallium-201
α	3.51 ± 3.48	6.19 ± 6.46
β	4.70 ± 3.81	6.62 ± 5.62
% successful	100% (50/50)	90.54% (67/74)

Good correlation was observed between the manual and automatically determined angles. Mean angular deviation reported corresponds to less than a 2 voxel offset. The analysis failed for only 7 of the 124 datasets due to significantly lower counts in the data. Average processing time per dataset was <30 sec. using modest computing power. These results indicate that this objective, standardized technique to automatically determine the LV long axis for SPECT reorientation is fast, accurate, robust and ready for clinical implementation.

No. 464

THE EFFECT OF SCATTER CORRECTION ON PERFORMANCE IN CLASSIFYING ALZHEIMER'S DISEASE PATIENTS AND NORMAL CONTROLS USING QUANTITATIVE SPECT.

M.F.Kijewski, K.A. Johnson, R.E. Zimmerman, J.A. Becker, R.J. English, A. Satlin, B.L. Holman. Brigham & Women's Hospital, Boston, MA.

Many approaches to scatter correction of SPECT images have been proposed, but consensus as to their relative merits has not been established. Most reported comparisons have been based on measures of image quality, such as resolution, or of image fidelity, such as mean square error. We report here the use of a measure of image utility, i.e., performance in a quantitative classification task, to evaluate a scatter correction method.

Tc-99m HMPAO SPECT brain images of 37 Alzheimer's disease (AD) patients and 63 normal subjects were collected on the CERASPECT™ brain imager. Each image was reconstructed both with and without application of the dual-window subtraction scatter correction method which is standard on the CERASPECT™. Images were registered and scaled to a common anatomic coordinate system. Analysis of covariance (ANCOVA) identified regions in which group differences in activity, normalized to occipital activity, were greatest. Five such regions were identified: a central region, left and right parietal regions, and left and right frontal regions. The performance of SPECT perfusion imaging in classifying AD and normal brains was measured both for scatter-corrected and uncorrected images using quadratic discriminant analysis of average counts within these five regions, normalized by the ANCOVA model to occipital activity. Per-formance was characterized by the area under a binormal ROC curve.

For classification using scatter-corrected images, the area under the ROC curve was 0.949 ± 0.021; without scatter correction, it was 0.847 ± 0.043. We conclude that scatter correction greatly improves performance even for an imaging task which relies on relative rather than absolute count data, and propose the use of quantitative classification tasks to compare scatter correction methods.

No. 465

ANALYSIS OF DIFFERENCE IMAGES CALCULATED FROM ICTAL AND INTERICTAL TC-99m-HMPAO SPECT SCANS OF EPILEPTIC SEIZURE PATIENTS.

I. G. Zubal, S.S. Spencer, K. Imam, J. Seibyl, E.O. Smith, G. Wisniewski, P.B. Hoffer, Yale University, New Haven, CT.

Image processing techniques were applied to SPECT brain images to aid in the localization of epileptic foci. Ictal and interictal cerebral perfusion SPECT images were acquired on 12 epilepsy patients (8 temporal, 4 extratemporal) after injection of 20mCi Tc-99m-HMPAO. Each ictal scan was registered to the same patient's interictal scan. A normalization of the 3D data was applied to account for global percent brain uptake and total injected activity. After registration, normalization, and subtraction of the SPECT images, functional difference images were computed which demonstrate areas of altered perfusion during ictus. Areas of elevated perfusion differences were identified as suspected areas of the primary (and secondary) seizure foci. Correspondingly, percent-change images were calculated, which give a quantitative measure of perfusion alterations during ictus.

The resulting difference images were also registered with each patient's MRI scan which permits a localization of perfusion changes onto anatomical structures. Areas in the brain, where strong perfusion differences occur, correlate with areas suspected to be seizure foci. A subgroup of patients monitored with implanted depth electrodes support this correlation.

When compared to side by side visual interpretation of the ictal and interictal SPECT images, registration of SPECT and MRI images together with calculated difference maps greatly enhances the ability to localize epileptic seizure foci. Single foci hyperperfusion during ictus consistent with EEG were discovered in all 4 extratemporal patients using this method. This offers the potential to locate epileptic seizure foci using a non-invasive and inexpensive imaging procedure and data processing algorithm.

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PROGRESS REPORT SUMMARY

As the present award approaches its third and final year, we are encouraged by the progress thus far achieved, the technical accomplishments of the current year, and the clear delineation of the tasks that remain in the coming period. Prior to reporting on these, we would like to point outthat there is a World Wide Web page devoted to this project in:

http://www.cc.gatech.edu/gvu/visualization/perfex/

This web page illustrates the salient characteristics associated with the knowledge-based system (PERFEX) developed under this award, such as its power in interpreting cardiac imagery and the degree of interactivity provided to the user. We would appreciate receiving any comments or questions regarding the information that appears in this site.

A. Specific Aims

The overall objective of this research is to develop computer-based methods to assist in the diagnosis of heart disease. More specifically, the overall goal is to explore, implement, and test knowledge-based approaches to interpret patient-specific information derived from images as well as other sources. The sources of information are textual (e.g., clinical symptoms), numeric (e.g., patient age, sex, and EKG results), and image-based (emphasizing cardiovascular nuclear medicine perfusion imagery, especially single-photon emission computed tomography (SPECT) using the tracers Tc-99m and Tl-201).

The approach combines various methods to accomplish these objectives, including computer vision, artificial intelligence, interactive computer graphics, and human-computer interaction principles. This approach has led to the formulation of PERFEX (for perfusion expert), a knowledge-based (KB) system that (a) infers structure (coronary vasculature implicated in disease) from function (myocardial perfusion), (b) combines spatial, temporal, and uncertainty reasoning models, (c) integrates symbolic (rule-based) with connectionist (neural network-based) methods, and (d) provides users with a highly interactive, graphical environment that supports queries and explanations. The specific aims are to:

(1) automatically determine the orientation of the left-ventricular (LV) myocardium from SPECT imagery;
(2) modify, extend, and refine the knowledge base to interpret the imagery;
(3) predict perfusion reversibility using artificial neural networks (ANNs);
(4) explore the interrelationships between symbolic (rule-based) and connectionist (ANN-based) methods.
(5) Test, validate and enhance the system's accuracy, robustness, and usability.

The original six aims have been collapsed into the above five. This has been done since the previous sixth task (usability testing) is closely linked to overall validation efforts, rather than separate from these efforts. Hence, the originally proposed work remains unchanged, while the tasks are presented as more closely integrated.

B. Studies and Results

Task 1: This task is completely finished, as summarized in the previous report. A Ph. D. dissertation and a high-quality journal publication have resulted from this work; in addition, the software for automatically determining orientation is being implemented in General Electric Medical System's SPECT systems.

Task 2: The major extension to the KB has been completed, which called for extending PERFEX from Tl-201 to Tc-99m MIBI. Using data from 461 patient studies, close to 300 rules were refined and verified for this purpose (see Am. Heart Assoc. publication). Furthermore, several enhancements and refinements have been made to increase overall robustness by including additional clinical information such EKG results, attenuation artifacts due to large chest size, chamber size, and lung uptake, as well as many other patient-specific clinical findings that are non-image based; a sample file containing some of this clinical information is enclosed (in Figure 1). These advances have resulted in the creation of two knowledge bases: one that has been "frozen" for extensive clinical validation (PERFEX I), and another one which will undergo further enhancements (such as the aforementioned ones; PERFEX II). Two journal publications have resulted from this work (see publications section E).

Task 3: The most significant technical breakthrough came in the task dealing with the prediction of perfusion reversibility. As summarized in last year's report, ANN training results had been encouraging while testing results were unacceptable. This problem has finally been overcome: one of the graduate students involved in the research, Eyal Schwartz, discovered that the inputs to the ANNs were improperly defined, and reformulated the problem using different input information and network topologies. The ANN has been successfully trained and tested with over 100 patient cases, such that perfusion reversibility can be accurately and consistently predicted. A journal manuscript has also emerged from this work, while others are planned.

Task 4: Since this task depended on the previous one (Task 4), only preliminary results are available. A promising approach to extract symbolic knowledge from the trained ANNs has been identified and implemented. We view the initial results with cautious optimism, and expect to focus on this task in the coming year.

Task 5: Extensive progress has been made in this area: an in-house validation effort was performed on the Tc-99m MIBI KB using 60 patient cases (30 males and 30 females). The results of testing with this population (and training with several hundred other cases) give consistently accurate results, as described in the Am. Heart publication. A second, clinically significant in-house evaluation was performed of the Tc-201 KB using 25 patient cases; this was a significant evaluation since the data had been previously interpreted by over 50 physicians reading at all levels of expertise. The validation confirmed that PERFEX could detect, localize, and interpret the information at the highest level of human expertise. More extensive validations are planned with completion prior to December 1995.

C. Significance

The results thus far obtained are significant from both clinical and scientific perspectives. The medical significance is five-fold: (1) the knowledge-based system (PERFEX) resulting from our research can aid in interpreting cardiac SPECT imagery in a consistently accurate manner; (2) the approach has been shown to be generalizable to two different perfusion agents (Tl-201 and Tc-99m MIBI); (3) the system becomes increasingly comprehensive and robust as other patient-specific, clinical (non-image) information is included in the decision-making process; (4) PERFEX provides users with justifications and explanations in an intuitive, interactive, and clinically meaningful manner; (5) PERFEX supports conducting only one imaging session on the patient (during stress), since the information thus derived is used (by a trained neural network) to predict reversibility distribution; and (6) the entire process, from image acquisition to interpretation, has been automated.

The technical significance is four-fold: (1) a robust approach has been developed to model the visual reasoning process associated with the interpretation of complex imagery (and other non-image information); (2) a highly novel method has emerged with which to predict one type of image (reversibility distribution) from other input images (stress perfusion distribution and percent thickening); (3) the knowledge-based system serves as a model regarding the integration of connectionist and symbolic methods; and (4) efforts are underway to discover ways to extract symbolic knowledge from connectionist architectures. This last effort represents a basic contribution to frontier research, as it would result in methods to extract knowledge (perhaps in the form of rules) from trained neural networks.

It is also noteworthy that this research has served as the basis for numerous publications, academic degrees, and, more recently, clinically useful software that is beginning to be licensed to medical imaging equipment manufacturers.

D. Plans

We will continue with enhancing the KB (Task 1) and refining the ANN for predicting reversibility distribution. However, the emphasis will be placed on Tasks 4 and 5, respectively: extracting knowledge from the trained ANN and validating the system. Regarding the latter, we have identified over 300 patient cases that have been studied using either Tl-201 or Tc-99m perfusion agents; all these patients have also undergone coronary catheterization. In addition, we are in the process of making the final preparations to export PERFEX I to other institutions to perform a multicenter validation and to document how well it compares with experts outside of the Emory system. Cedars-Sinai Medical Center in Los Angeles will be the first sight. Implementation and evaluation is expected by January 1996. We expect to bring all specific aims to completion by January 1997.

E. Publications

"Advanced Computer Methods in Cardiac SPECT" (book chapter), C. D. Cooke, T. Faber, and E. V. Garcia, in Cardiac SPECT Imaging, E.G.DePuey, D.S. Berman, and E.V. Garcia, eds.; Raven Press, Ltd., New York, NY, pp. 75-89 (1995).

"Automatic Determination of LV Orientation from SPECT Data," R. Mullick and N. Ezquerra, IEEE Transactions on Medical Imaging, Vol. 14, No. 1, March 1995.

"Expert System Interpretation of Technetium-99m Sestamibi Myocardial Perfusion Tomograms: Enhancements and Validation," E. Garcia, D. Cooke, E. Krawczynska, R. Folks, J. Vansant, L. de Braal, R. Mullick, and N. Ezquerra, Proc. American Heart Assoc. Conf., Anaheim, CA, Nov. 1995.

"Topological Goniometry: An Approach to Orientation Determination of Cylindrical Objects," N. Ezquerra and R. Mullick, accepted for publication in ACM Transactions on Graphics (1996).

"A Connectionist Approach to Image Prediction," N. Ezquerra, L. de Braal, E. Schwartz, D. Cooke, and E. Garcia, IEEE Trans. on Medical Imaging manuscript.

"A Knowledge-Guided Approach to Tomographic 3D Image Visualization," N. Ezquerra, L. de Braal, E. Garcia, and D. Cooke, IEEE Trans. on Comp. Graphics and Visualization manuscript.

"Integration of Symbolic and Connectionist Approaches," E. Schwartz, Internal Report (basis for IEEE TMI manuscript above) (1995).

"Inteligencia Artificial en Medicina" (book, published in Spanish), ISBN 84-88051-42-5, Colección Informática No. 3-1994. Fundación A. Brañas, Publisher, Santiago de Compostela, Spain (1995)

"Visualization of Medical Imagery," (electronic publication), ACM Special Interest Group on Biomedical Computing (SIGBIO), CD-ROM, Vol. 14, No. 3.

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B. BACKGROUND AND SIGNIFICANCE

B.1 Overview: It is well recognized that heart disease has always been, and remains, a central health care problem. As observed by Pasternak, Braunwald and Sobel, "Heart disease continues to be the number one killer in the U.S., with 25% of all deaths related to coronary artery disease" [Pas92]. Furthermore, heart disease seriously affects the lives of millions: there are 1.5 million myocardial infarctions in the U.S. per year [Pas92, Kit88]. This deadly disease is not only costly in terms of irreplaceable human life, but also represents a significant economic factor in terms of staggering health care costs and overall loss of productivity. As a consequence of these considerations, the process associated with the prevention, detection, and treatment of heart disease remains one of the greatest concerns in all of health care. This process, in turn, relies on the careful acquisition and interpretation of significant amounts of medical and clinical information.

It would appear that such an important and information-intensive process should benefit from emerging computer- and information-based technologies, as these powerful technologies are, in fact, designed to process large amounts of information accurately, reliably, and efficiently. It is in this broad context that the present application seeks to make a contribution: through the exploration of frontier computing methods aimed at supporting and facilitating the decision-making process associated with assessing heart disease. The discussions that follow will further elaborate on this basic theme, focusing on specific, technical issues of the underlying medical and computer sciences. We begin in Section B.2 with a discussion of SPECT imaging, its clinical relevance, and the benefits of employing computational methods to represent medical knowledge, reasoning models, and human-computer interaction principles. Section B.3 then addresses the importance of myocardial thickening, and the value of invoking methods of artificial neural networks to extract and discover knowledge. Section B.4 underscores the significance of integrating PET imagery in the decision-making process, while Section B.5 gives a final summary of research efforts related to those presented in this application.

B.2 Cardiovascular SPECT Perfusion Imaging: Relevance and Challenges: Clinical decisions regarding heart disease depend on the accurate and reliable assessment of coronary artery disease (CAD). In particular, decisions concerning a patient's diagnosis, therapy and prognosis are based primarily on two factors : (a) the extent and severity of atheromatous obstruction (i.e., a blockage or stenotic lesion in blood vessels) and (b) the degree of functional impairment caused by diseased myocardium (heart muscle) [Bru73a, Bru73b, Das77, Har79, Har80, Hum74, Lea81, Moc82, Rin83, Rou83a, Rou83b]. The "gold" standard for assessing the extent and severity of atheromatous obstruction is coronary angiography (X-rays of coronary arteries enhanced by a contrast medium) [Gou86], a standard that we will employ in our evaluation methods. On the other hand, tomographic perfusion (blood flow) imaging of the left ventricular (LV) myocardium, particularly SPECT imaging, is used as the "gold standard" in predicting not only blood flow to a myocardial region but also the amount of normal myocardium versus jeopardized but viable (ischemic) or infarcted (dead) myocardium, and remains the most widely accepted and preferred non-invasive imaging technique for assessing myocardial perfusion characteristics [DeP89].

Hence, myocardial SPECT imaging is an essential and routinely used process in assessing CAD. Currently, approximately three million patients per year are studied using myocardial perfusion studies in the United States, of which it is estimated that 80% use SPECT [DeP95]. The objective of this research is precisely to facilitate and support the interpretation of myocardial imagery. To further illustrate the importance, timeliness, and difficulties associated with this objective, it would be worthwhile to briefly describe some of the salient characteristics associated with this clinical information. Figure 1 shows a typical set of perfusion studies for an individual patient. Each of the nine images in this figure is a polar representation of the three-dimensional (3D) myocardial perfusion information, extending from the apical region (center of the polar map) through the basal region (outermost circumference of the polar map) of the heart. The polar maps (also called "Bull's Eye" plots) are processed, quantified, and color coded using a color table that maps those areas containing relatively high concentrations of radioactive tracer (i.e., higher perfusion levels) into bright colors (e.g., yellow and orange), while those areas that contain relatively low tracer concentrations when compared to "normal" patient populations (and thus represent regions of hypoperfusion, or perfusion "defects") are mapped into darker colors (e.g., magenta and blue) [Coo90, DeP88]. In Figure 1, the images along columns correspond to stress (ST; patient at exercise), delayed (DL; patient at rest, hours after exercise), and reversibility (RV, normalized difference between the delayed and stress distributions); stress images are useful in determining perfusion defects in general (and infarctions in particular), while delayed images are useful in determining possible perfusion redistribution (i.e., ischemia, indicating viable myocardium). Along the rows of Figure 1, the images correspond to raw, blackout (BO, wherein regions beyond 2.5 standard deviations from normal limits are set to a pixel value of zero), and standard deviation information (SD; deviation from normal limits).

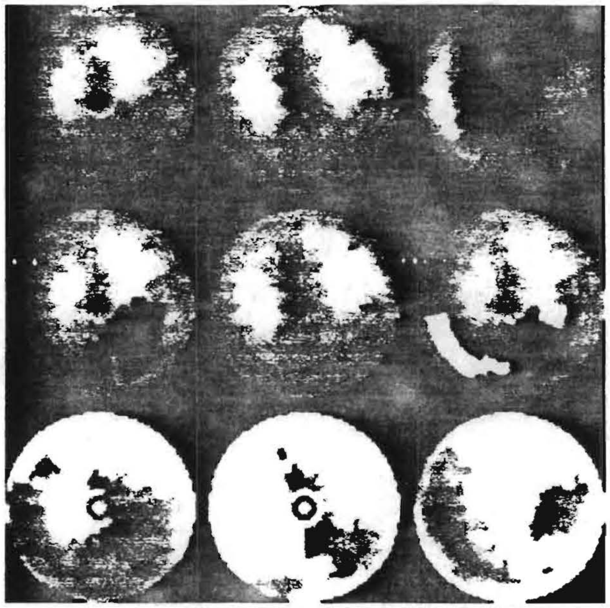

FIGURE 1. Polar representation of SPECT perfusion information.

Figure 1 appropriately suggests that well established techniques are available and routinely used to display and quantify myocardial perfusion, thereby providing a mechanism for expressing the location, extent, and severity of perfusion defects and perfusion reversibility. [DeP88, DeP89, Coo90, DeP95]. Through extensive training and experience, clinicians can learn to interpret this information by visually detecting, characterizing, and interpreting the imagery, and subsequently mentally integrating this visual information with other relevant, clinical data.

There are, however, a number of significant challenges and difficulties associated with performing this diagnostic task of interpreting image and non-image information. Clearly, the amount of the information can be overwhelming. The images are numerous, encompassing raw images, comparison images, images associated with the temporal effects of redistribution, etc. Moreover, non- image information must also be taken into account. This brings up an issue of major concern. As the health care environment evolves, clinicians are expected to interpret these studies with the highest accuracy possible (avoiding incorrect interpretations that promote other costly procedures) and in the least time as possible (also reducing cost). Yet, at the same time, these clinicians are faced with ever-increasing amounts of information. In the proposed research, we will address performance, efficiency, and information overload issues in various ways.

One important way is by capturing and representing domain knowledge to facilitate the interpretive task, and providing further support by imbedding this knowledge into an intuitive, useful, and usable interface that is directly integrated into the clinicians' working environment. The underlying hypothesis is that diagnostic interpretation performance can be both supported and significantly improved by providing assistance to the user through reduced workload, task analysis considerations, and the use of domain knowledge. The basis for this hypothesis is an emerging body of knowledge showing that principles and methods of artificial intelligence (AI), scientific visualization, and human-computer interaction (HCI) can be invoked to guide and facilitate this information-intensive, interpretive task [Man94, Kle89, San89a, McC87, Cle85, Tuf83, Mar93, Mas91, Shn87, Mac86, Cha73, Rot94, San89b, Ezq93]. This approach is further validated by evidence supporting the concept that computer quantification of myocardial perfusion images improves not only the overall diagnostic yield but also enhances reliability, accuracy, confidence and reproducibility of interpretation [Wac94]. Thus, the approach is undergirded by principles and methods of AI, HCI, and scientific visualization. Specifically, in Aim #1, we extend our previous efforts to achieve more comprehensive and accurate diagnostic decisions by (i) fusing probabilistic and heuristic methods to model a priori likelihood of CAD [Dia79], and (ii) by including all vital, non-imaging variables that experts normally apply [Kra95]. Additionally, in Aim # 3, we will develop data mining, query, and search strategies to facilitate CAD assessment through an intelligent database design.

Another difficulty with interpreting the perfusion information is that typically this information is displayed in formats that are not intuitive: as suggested in Figure 1, the images are presented as a series of polar maps which are clearly distorted representations of 3D perfusion distributions, similarly to the way in which the Earth's true surface is distorted in a 2D Mercator projection. These considerations create a significant visual workload even for experienced physicians. The degree of difficulty associated with this demanding and ill-defined task is reflected in the observation that medical experts can sometimes prefer certain types of display formats over others, believing the selected formats to be optimal, despite the fact that tests of their own visual performance indicate otherwise [Gil89]. We will directly address these concerns in Aim #1 by creating an intuitive UI using well-established HCI and visualization principles [Fol90, Loh90, Mar93, Shn87].

A further challenge is the lack of standardization and related inter-observer and intra-observer variabilities. Standardization is difficult as the visual interpretation process involves complex interrelationships between the observer, the characteristics inherent in the information, and other factors such as task definition, level of expertise, and the interaction environment [Kle89, San89a, Cle85, Ras86, Tuf83, Mar93, Shn87]. Because of the wide variability in the training that physicians have in interpreting these studies [Cer94], there is a wide variability in the accuracy of how these studies are interpreted [Kra96]. It is recognized that diagnosticians with less expertise tend to fail to recognize imaging artifacts and clinical variables and interpret at lower levels of specificity [DeP89][Kra96]. It has also been pointed out that a trained observer can disagree with his or her own diagnostic interpretation (when presented with the same image information) as much as 15% of the time [Con82]. In addition, physicians with less experience in interpreting perfusion imagery may be required to make diagnostic decisions without the supervision of clinical experts. We consider these challenges in Aims #1 and #2, by (i) creating a UI based on an iterative design process conducted with the aid of a diverse group of users, and (ii) conducting extensive evaluation studies in a multicenter setting and through prospective and retrospective trials designed by our biostatistician (Clark). The PI (Ezquerra) and Co-PI at Emory (Garcia) will orchestrate communications between, and visits to, the external centers in order to conduct these analyses.

Yet another challenge is that the interpretation task involves inferring structure from functional information. This is the case because the images provide information about the presence (or absence) of perfusion defects in the myocardium, and this information can also be viewed as providing indirect evidence of obstructions (lesions) in the coronary vessels, since the perfusion defects can result from coronary arteries that cannot properly perfuse the myocardium. The images therefore provide direct information about the myocardial perfusion distribution, and indirect evidence of coronary artery disease. In this sense, the imaging procedure measures functional or physiological information (LV myocardial perfusion) from which structural or anatomical information (possible sites of arterial disease) can be inferred. This process of inferring structure from function is also not standardized, requires extensive training and experience [DeP95], and calls for spatial reasoning models. Moreover, the temporal effects of perfusion redistribution call for models of temporal reasoning in order to address the issues associated with delayed image acquisition. We directly address these issues in Aims #1 and #2 by capturing and representing the visual reasoning process employed by experts in making these spatial and temporal inferences (in both SPECT and PET imaging), using relevant AI methods [Neb95, All84, Kah85, Ton92].

B.3 Myocardial Thickening: A serious challenge to nuclear cardiology (actually to all diagnostic modalities) in the current cost-conscious environment is to provide an increased amount of clinically important information with minimal or no increase in cost [Ber95]. With the advent of Tc-99m SPECT perfusion agents, F-18 metabolic agents, and new instrumentation to perform electrocardiographic (ECG) synchronized tomographic imaging, ventricular function and perfusion metabolism can now be assessed with a single injection of a radiopharmaceutical [Gar94a, Gar94b, Ber95]. We have shown [Gal90] that, due to partial volume effects [Hof79], the change in myocardial counts throughout the cardiac cycle is proportional to the change in myocardial thickness [Coo94]. This proportionality has been used in both PET [Bom96] and SPECT [Chu94] for the assessment of regional myocardial thickening. If resting myocardial thickening is measured simultaneous to assessing the myocardial stress perfusion distribution (dose injected at peak stress but imaged at rest), then determination of ischemia, scar and viable myocardium in a single setting would be possible [Gal83, Gal84, Zif91].The clinical importance of this finding is that acquisition time, cost and morbidity could be considerably reduced. Thus, the use of myocardial thickening information in conjunction with stress perfusion information can serve as a measure of the redistribution of perfusion in viable (but infarcted) myocardial tissue.

Unfortunately, the patterns of the rate of thickening, as well as the interpretation of the thickening and stress information together, represent a relatively new and complex interpretation problem. To address these considerations, machine learning methods appear to offer a viable and computationally efficient approach to assist in the analysis, processing, and interpretation of this complex information. Machine learning methods have evolved over the past several years as a way with which to create systems that can discern complex image patterns in a manner that is relatively accurate, generalizable, computationally efficient, and robust with respect to noise and data variations [Rum86]. In particular, artificial neural networks (or, equivalently, connectionist systems) provide a means of creating algorithms that can be trained to extract patterns from complex images and subsequently discern similar patterns in newly encountered imagery [Her91, Mar90, Mul90]. Thus, an artificial neural network (ANN) may enable prediction of redistribution perfusion from images associated with myocardial thickening and stress perfusion. Based on this hypothesis, we have begun exploring such a connectionist system with encouraging success, as described in more detail in Section C.

We will build on these results to conduct deeper and even more creative experiments in Aim #1 of the current application. In a number of ways, these studies are novel and of consequence. As previously noted, the requirement of only a single clinical test to obtain the information represents reductions in costs, risks, and discomfort. A second, highly original aspect of this work is that connectionist (ANN-based) methods will be used to predict one kind of image (reversibility) from other input images (stress perfusion and myocardial thickening). Another, computationally innovative aspect is that we will investigate methods for extracting knowledge from trained ANNs (designed to predict reversibility), and use this knowledge to gain a deeper understanding of the relationship between perfusion reversibility and myocardial thickening [Ezq93, Gal83, Gal84, Zif91]. Furthermore, we will investigate ways to discover new knowledge through the use of unsupervised, associative-memory learning methods (self-organizing, Kohonen-type architectures) [Koh82, Mur95, Her91, Mar90, Mul90].

Also of significance is the integration of symbolic and connectionist approaches into a coherent computational framework. Historically, the symbolic-logic branch of AI (e.g., rule-based approaches) and the connectionist evolved separately: the former viewed as a "functional" approach to problem-solving and learning inspired by neurophysiological models of reasoning and behavior, whereas the latter emerges as a model of neural processing and may be regarded as the "structural" approach to cognition. It is only very recently that there has been interest in the possible integration of, and the interrelationships between, these two paradigms [Cra94, Opt93, Opt94, Sha92, Tow93, Tow94]. Hence, the relevance of this project lies in exploring ways to achieve this integration and in possibly obtaining a deeper understanding of these interrelationships, which may have an impact in a number of areas including AI, cognitive science, and learning and memory.

B.4 PET Imaging: To further improve diagnostic accuracy, the current application will also introduce another imaging modality. Ultimately, decisions regarding how to treat a patient with CAD are related to whether the myocardium affected is viable, and to whether a particular treatment would recover or preserve ventricular function. The role of positron emission tomography (PET) is critical in this decision making process. Numerous diagnostic imaging modalities have been investigated for determining myocardial viability. These techniques include contrast ventriculography, echocardiography, radionuclide ventriculography, and MRI techniques. The most widely used technique continues to be thallium-201 scintigraphy, one of the tracers that can be interpreted by our current knowledge-based system (as discussed in Section C). However, even in the hands of experts, this imaging technique overestimates nonviable myocardium in 30-40% of the patients [Dil90].

Fluorodeoxyglucose (FDG) PET imaging is the approach of choice for the evaluation of myocardial metabolism, particularly where the clinical concern of viability is an issue [Mar83, Til86]. FDG accumulates in the heart in proportion to glucose utilization by the myocardial cells, serving as a marker for cell viability. The normal healthy heart uses free fatty acids for its energy needs. In the presence of ischemia, metabolism shifts to glucose. Therefore in an ischemic condition, perfusion is diminished and the FDG-PET study shows normal or increased glucose metabolism implying ischemic but viable myocardium. These studies correlate well with the eventual return of myocardial contractility and function after revascularization in areas of segmental ischemia and viability. The absence of FDG uptake in the myocardium is consistent with infarction and nonviable tissue. The results of a cardiac study including perfusion (with any of the PET {ammonia or rubidium} or SPECT (Tl-201, Tc-99m-sestamibi, etc) and FDG for viability can have a significant impact on clinical decision and management. Thus, Aim #2 is devoted to extending our knowledge-guided interpretation approach to this new modality, and to use this modality as additional, valuable information to be fused with the perfusion and functional imagery (SPECT) information. Additionally, since myocardial contractility is synonymous with viability, the information extracted from EKG synchronized multiple gated FDG acquisitions will be classified using ANNs, also in Aim #2.

B.5 Related Research: As the foregoing discussions suggest, the clinical assessment of CAD may be viewed as an information- and knowledge-intensive task that requires extensive experience, the integration of visual and non-visual data, and the extraction of structural inferences from information that is primarily functional in nature. From a broad perspective, the task involves complex interrelationships between perceptual, cognitive, and human-computer interaction variables. As noted earlier, there is increasingly compelling evidence that principles and methods of artificial intelligence, scientific visualization, and human-computer interaction can be invoked to facilitate such information-intensive, interpretive tasks [Man94, Kle89, San89a, McC87, Cle85, Tuf83, Mar93, Shn87, Mac86, Cha73, Rot94, San89b, Ezq93]. The use of these principles, especially computer-based methods, can be traced back several decades [Sch38, Led59, Lip61, Gor73, Buc84, Pop81, Wei78, Pat81]. Since this body of knowledge is well known and well documented, we will limit the present discussions to a brief analysis of recent work concerned with interpreting cardiac imagery, and contrast these methods to our approach.

It was observed earlier that our approach can be viewed as knowledge-guided rather than knowledge-based, since the latter usually denotes a specific knowledge representation paradigm (e.g., rule-based techniques), whereas our approach utilizes domain knowledge symbolically as well as through other mechanisms (including connectionist, probabilistic, and temporal reasoning techniques). Our methods are thus distinct from other approaches in a number of ways. In contrast to some model-based methods which look at heart physiology and function by considering arrhythmias and ECG information [Wid92, Ton93], the proposed research considers some of this information (e.g., clinical ECG results) while also taking into account image information. In terms of image interpretation, a number of investigators have researched the interpretation of cardiac imagery by using ANN methods [Por94, Ham95, Fuj92], by considering the intelligent processing of LV wall motion or some subset of the imagery [Dun84, Tso85], by emphasizing a particular method of uncertainty reasoning [Ros86], or by using rule-based [Rei87, Hor90, Nie85] or case-based [Had95] models. There are several limitations associated with these approaches. One is that a single reasoning or knowledge representation method is used. Consequently, ANN-based approaches remain "black boxes" that do not easily yield any insights or knowledge, while rule-based and case-based approaches suffer from knowledge-acquisition bottlenecks and/or KB or case-base incompleteness. In the proposed research, however, the thrust is placed on considering the overall diagnostic process rather than a component of this process, and the emphasis is placed on the ensemble of the imagery (stress, delayed, etc.) as well as other clinical information. Moreover, our approach combines connectionist and symbolic-logical approaches, thereby exploiting the respective strengths of the two paradigms, and integrating these with temporal and probabilistic reasoning techniques to create a more comprehensive visual reasoning model.

There are other, important distinctions. The proposed work will build on our success with SPECT image interpretation to integrate PET imagery. Additionally, the methodology utilizes the information associated with myocardial thickening. And, to further facilitate the decision-making process, HCI and human factors principles form an integral part of the overall system development. None of the approaches reported in the literature encompass these features. Figure 2 shows a schematic diagram representing the comprehensive, interdisciplinary nature of our approach, depicting some of the salient aspects of the constituent methods. The approach shown in Figure 2 is grounded on our previous research, which discussed in detail next, in Section C.

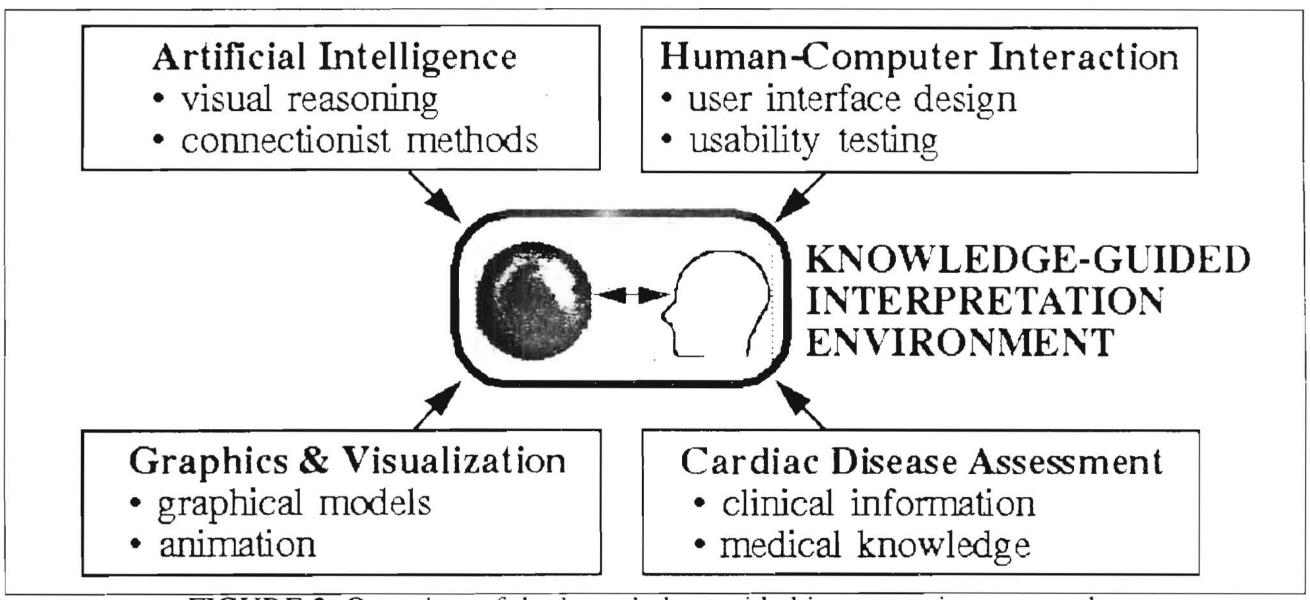

FIGURE 2. Overview of the knowledge-guided interpretation approach.

C. PROGRESS REPORT

The present report covers the three-year period 02/01/94 through 01/31/97. It should be observed that, as we write this report, we are only beginning the third year of this period and thus the report essentially covers the previous two years (2/94 through 2/96). The overall objective of the research has been to develop computer-based methods to assist in the diagnosis of heart disease. In particular, the thrust of the research has been to develop methods for assisting in the diagnostic interpretation of cardiovascular 3D imagery. As previously noted, the interpretation of complex medical imagery is an information-intensive task that typically requires expediency, accuracy and reliability in both the presentation as well as in the interpretation of the visual information. Our approach facilitates this task by invoking artificial intelligence, visualization, and human-computer interaction principles to (a) extract the relevant information from the imagery, (b) assist in the interpretation of image and relevant non-image information, and (c) create a useful, intuitive, and usable working environment for clinical decision-making. The specific aims for the 94-97 period are as follows:

(1)to automatically determine the orientation of the left-ventricular (LV) myocardium from SPECT imagery (such that the data set is properly aligned with respect to the natural LV axis);
(2)to modify and extend, a previously created KB to interpret the imagery (to increase robustness and accuracy);
(3)to predict perfusion reversibility using ANNs (such that only one image acquisition is necessary);
(4)to extract knowledge from trained ANNs (to integrate connectionist and symbolic (rule-based) methods); and
(5)to test, validate and enhance the system's accuracy, robustness, and usability.

Prior to discussing the progress associated with each of the above specific aims, it would be worthwhile to give a broad overview of the nature of our accomplishments, which may be viewed as four-fold: (i) academic (degrees obtained by individuals working on the project); (ii) scholarly (publications, reports, presentations, and dissemination of results); (iii) intellectual (technical results, insights, and contributions made to the body of knowledge; and (iv) practical (clinical implementation of the methods and software resulting from the research).

The subsequent discussions describe these accomplishments in more detail. We begin by first summarizing the medical and scientific significance of the results in Section C.1; Section C.2 describes academic accomplishments; Section C.3 lists publications and other scholarly contributions; and Section C.4 summarizes technical and intellectual achievements. It is important to note that Section C.4 is somewhat extensive, as it discusses technical issues and low-level details that are crucial for our proposed research. Thus, the discussions of Section C (particularly Section C.4) should be viewed as an integral part of the methods and experimental design issues that are continued or expanded on in Section D.

C.1 Overall significance of accomplishments: The results thus far obtained are significant from both clinical and scientific perspectives. There are several points of medical significance: (1) the knowledge-guided methods resulting from our research can aid in interpreting cardiac imagery in a consistently accurate manner, thereby facilitating this information-intensive task; (2) the approach has been shown to be generalizable to different perfusion agents, giving the approach greater clinical usefulness; (3) the interpretation system resulting from our research has become increasingly comprehensive, robust, and useful as other patient-specific, clinical (non-image) information is included in the decision-making process; (4) a user interface (UI) has been designed, implemented, and evaluated, which provides users with timely, intuitive, and practical support within the normal, clinical environment, and which provides justifications and explanations in a highly interactive manner; (5) the interpretation system integrates both stress and delayed (reversibility) information; (6) the entire process, from image acquisition through interpretation, has been almost completely automated, resulting in a valuable and practical clinical tool; and (7) extensive tests and evaluation experiments have been conducted both internally and externally.

Numerous milestones of technical significance have also been reached: (1) a robust approach has been developed to model the visual reasoning process associated with the interpretation of complex information; (2) a highly innovative method has emerged with which to predict one type of image (reversibility distribution) from other input images (stress perfusion distribution and percent thickening) through ANNs; (3) a method for automatically determining the orientation of a 3D object (LV myocardial mass) imbedded in a 3D data set (SPECT imagery) has been created, and has subsequently been generalized to other medical and non-medical domains; (4) the approach infers structural information from functional information; and (5) preliminary results demonstrate the viability of extracting symbolic knowledge from connectionist architectures.

C.2 Academic Accomplishments: It is important to observe that this grant has supported several individuals who either have obtained, or are in the process of obtaining, advanced (graduate) degrees through their work on this research. One student (Rakesh Mullick), received a Ph.D. degree from The Georgia Institute of Technology (Georgia Tech) August 1994; Rakesh's dissertation was in fact the subject of specific aim #1 above (orientation determination). Two students received Master's degrees: Eyal Schwartz (M.S. June 1995, Georgia Tech), whose work was in ANNs (aim #3), and Levien de Braal (M.S. July 1994, Technical University of Delft, The Netherlands), whose user interface (UI) design and usability studies (aim #5) defined his thesis theme. In addition to the degrees granted to these individuals, three other graduate students have also significantly contributed to the project; two of these remain degree candidates in Georgia Tech's Ph.D. program (James

O'Brien and Thomas Browne) while the third contributor (Joaqu¡n Madrid) will earn his degree in Spain.

Moreover, this research project has benefitted from the contributions of three post-doctoral scientists who visited Georgia Tech from universities in Spain during the 1992 academic year: A. Pazos, M.D.-Ph.D., V¡ctor Maojo, M.D.-Ph.D., and F. Mart¡n, Ph.D. The work conducted by these post-doctoral fellows (primarily related to aims #2, #3 and #4) came at no cost to the project, as Doctors Pazos, Maojo and Mart¡n were funded by the Spanish government. Thus, the project not only benefitted from their contributions, but also served as a vehicle through which to enhance their professional careers. The research conducted by these post-graduate researchers, as well as that conducted by the students, was supervised by the PI (Ezquerra) and resulted in numerous (approximately 30) publications, as can be appreciated from the list included in this report (Section C.3).

This grant has therefore been an invaluable financial and intellectual framework for the development of the careers of several outstanding young researchers, serving as a source of theses and/or dissertation topics leading to graduate degrees, as a challenging project to post-doctoral fellows, and even as a vehicle through which interinstitutional and international ties (between Georgia Tech, Emory University, and universities in Spain and The Netherlands) have been strengthened. It is also noteworthy that one of the aforementioned individuals, Levien de Braal, has been hired as a Research Scientist to continue his outstanding work in this research.

C.3 Scholarly Contributions: Publications and Dissemination of Knowledge; In terms of intellectual contributions, the findings and results associated with this research have contributed toward the body of knowledge associated with knowledge-guided interpretation of medical imagery and models of visual reasoning. In particular, our research findings span the areas of computer vision, AI, HCI, and cardiovascular diagnostic imaging. It should be stressed that this publications list is not merely large (approximately 30 publications), but it is also of high quality and encompasses two important medical informatics communities: the community of computer scientists and engineers, and the community of medical scientists and clinical researchers. Appendix B contains reprints of several of the following papers.

"PERFUSE: A Medical Expert System User Interface Prototype," Master's Thesis by L. de Braal, ID. # 115341, Dept. of Information Systems, Delft U. of Technology, Delft, The Netherlands, April 1995.

L. de Braal, N. Ezquerra, E. Schwartz, C. D. Cooke, and E. Garcia, "Analyzing and Predicting Images Through a Neural Network Approach," submitted to 1996 Vis. in Biom. Comp. (VBC '96) Conf., 10/96, Hamburg.

C. Cooke, E. Garcia, S. Cullom, T. Faber and R. Pettigrew, "Determining the Accuracy of Calculating Systolic Wall Thickening Using a Fast Fourier Transform Approximation: A Simulation Study Based on Canine and Patient Data," J. Nuc. Med. Vol. 35, No. 7, pp. 1185-1192, 1994.

"Advanced Computer Methods in Cardiac SPECT" (book chapter), C. D. Cooke, T. Faber, and E. V. Garcia, in Cardiac SPECT Imaging, E.G. DePuey, D.S. Berman, and E.V. Garcia, eds.; Raven Press, Ltd., New York, NY, pp. 75-89 (1995).

N. Ezquerra, "Medical Informatics at Georgia Tech," Gold Medal-winning (first place) poster presented at MEDINFO 92 (International Medical Informatics Conference), Geneva, Switzerland, Sept. 1992.

N. Ezquerra, "Connectionist Methods in Medicine," invited presentation at the International Congress on Knowledge Engineering, Seville, Spain, October 1992.

N. Ezquerra, R. Mullick, D. Cooke, E. Krwyszenska, and E. Garcia,"PERFEX: An Expert System for Interpreting Perfusion Images," invited paper, Expert Syst. With Apps., Vol. 6, pp. 459-468, 1993.

"Visualization of Medical Imagery," ACM Special Interest group on Biomedical Computing (SIGBIO) CD-ROM, Vol. 14, NO. 3, September 1994.

"Inteligencia Artificial en Medicina" (book, in Spanish), N. Ezquerra and A. Pazos, ISBN 84-88051-42-5, Colecci¢n Inform tica No. 3-1994. Fundaci¢n A. Bra¤as, Pub., Stgo. de Compostela, Spain (1995)

"Visualization of Medical Imagery," (electronic publication), ACM Special Interest Group on Biomedical Computing (SIGBIO), CD-ROM, Vol. 14, No. 3.

"Topological Goniometry: An Approach to Orientation Determination of Cylindrical Objects," N. Ezquerra and R. Mullick, accepted for publication in ACM Transactions on Graphics (1996).

"Knowledge-Guided Visualization of 3D Medical Imagery" N. Ezquerra, L. de Braal, R. Mullick, D. Cooke, E. Krawczynska and E. Garcia; submitted to IEEE Trans. Visualization and Comp. Graph.

"Model-Guided Segmentation of Sparse, 3D Imagery," N. Ezquerra and R. Mullick; submitted to CVGIP: II.

Folks R, Garcia E, Van Train K, Areeda J, Berman D, DePuey E: Quantitative Two-day Sestamibi Myocardial SPECT: Multicenter Trial Validation of Normal Limits. (Submitted, 1996 annual meeting, SNM)

E. Garcia, "Myocardial Perfusion SPECT Imaging: Quo Vadis?," J. Nuc. Card., Vol. 1, No. 1, pp. 83-93, 1994.

"Assessment of Mechanical Function as an Adjunct to Myocardial Perfusion/Metabolism Emission Tomography Studies," J. Nuc. Med., Vol. 35, No. 6, June 1994.

"Expert System Interpretation of Technetium-99m Sestamibi Myocardial Perfusion Tomograms: Enhancements and Validation," E. Garcia, D. Cooke, E. Krawczynska, R. Folks, J. Vansant, L. de Braal, R. Mullick, and N. Ezquerra, Circulation, Vol. 92, No. 8, October 1995.
Garcia EV, Krawczynska EG, Folks RD, Cooke CD, Ezquerra NF: Expert System Interpretation of Myocardial Perfusion Tomograms: Validation using 288 Prospective Patients. (Submitted, 96 SNM meeting).
M. Herbst, E. Garcia, D. Cooke, N. Ezquerra, R. Folks, and G. DePuey, "Myocardial Ischemia Detection by Expert System Interpretation of Thallium-201 Scintigrams," in Cardiovascular Nuclear Medicine and MRI, (J. Reiber and E. Van der Wall, eds.), Kluwer Academic Publishers (1992).
E. Hyche, N. Ezquerra, and R. Mullick, "Spatiotemporal Detection of Arterial Structures Using Active Contours," Proc. 2nd. Int. Conf. on Vis. in Biom. Comp.; pp. 56-62, Chapel Hill, NC, October 1992.
"Three-Dimensional Coronary Angiography," J. Klein, J. Peifer, E. Garcia, C. Cooke, R. Folks, N. Ezquerra, and S. King; Am. J. Cardiac Imaging Vol. 7, No. 3, pp 187-194 (1993).
E. Krawczynska, N. P. Alazraki, W. Clark, et al., "Effect of Physician Training on Performance of Interpreting Cardiac Tl-201 SPECT Studies: Comparison to Expert System Results," submitted, SNM Meeting, CO, 6/1996.
J. Madrid, R. Mersereau, and N. Ezquerra, "Topological Considerations on Grey Level Skeletonization," Proc. Conf. on Visual Comm. and Image Processing, SPIE V. 1818, p. 392-401, Boston, MA.
Joaqu¡n Madrid, M.S. GIT 1995 (ECE); thesis: "Morphological Image Processing" to be defended at Universidad de Sevilla, Spain, Su96.
R. Mullick, N. Ezquerra, E. Garcia, and D. Cooke, "3D Visualization of Pose Determination in SPECT Imaging," Proc. VBC '92; SPIE 1808 pp. 445-54; Chapel Hill, NC, October 1992.
"Clinical Evaluation of Automated Technique to Reorient Left-Ventricular Myocardium in Cardiac SPECT," Journal of Nuclear Medicine, Vol. 35, No. 5, R. Mullick, D. Cooke, and E. Garcia, 1994.
R. Mullick, received Ph.D. in ECE in 1994; thesis: "Determination of the Orientation of the Myocardium in SPECT Imaging." Presently a member in the Inst. of Systems Science, Nat. U. of Singapore.
"Automatic Determination of LV Orientation from SPECT Data," R. Mullick and N. Ezquerra, IEEE Transactions on Medical Imaging, Vol. 14, No. 1, March 1995.
J. O'Brien and N. Ezquerra, "Automated Segmentation of Coronary Vessels in Angiographic Image Sequences Using Temporal, Spatial, and Structural Constraints," VBC 94, SPIE Vol. 2359, No. 25, pp. 25-37, 10/1994.
"Image Segmentation Using Geometric, Physical, and Temporal Constraints," N. Ezquerra and J. O'Brien, submitted to Machine Vision and Applications.
A. Pazos, N. Ezquerra, F. Martin, and V. Maojo, "A Neural Networks Approach to Medical Image Interpretation," Proc. World Congress on Med. Info. (MEDINFO '92); Geneva, Switzerland, Sept. 1992.
J. Peifer, E. Garcia, D. Cooke, J. Klein, R. Folks, and N. Ezquerra, "Visualization of Multimodality Cardiac Imagery," Proc. VBC '92; pp. 225-233; Chapel Hill, NC, October 1992
"Integration of Symbolic and Connectionist Approaches," E. Schwartz, Internal Report (1995). (Appendix B.4)
K. Van Train and B. Berman, Report on the results of the extramural evaluation of PERFEX; Internal Project Report; also attached as Appendix ZZB1.
K. Van Train and B. Berman, Report on the results of the extramural evaluation of the user interface of PERFEX; Internal Project Report; also attached as Appendix ZZB2.
[WWW] World Wide Web entry: http://www.cc.gatech.edu/gvu/visualization/perfex/

C.4 Technical and Intellectual Accomplishments: In the following, we discuss specific technical and intellectual accomplishments achieved during the previous two-year period. The discussions are cast in terms of the five specific aims as well as in relation to the research proposed in the current application.

Overall, we conclude that we have met, or are meeting, our specific research aims. There has been excellent progress with respect to Aim #1 (orientation determination), Aim #2 (refinements of the KB to increase robustness and accuracy), and Aim #3 (reversibility prediction using neural networks); and good progress in relation to Aim #4 (knowledge extraction from ANNs). Aim #5 (testing and evaluation, which has been integrated into each of the previous four aims) has been a major, continuing effort: our methods have been thoroughly and systematically tested and evaluated both by our institutions as well as by another center (Cedars Sinai Medical Center, Los Angeles, CA). It is again observed that, as of the writing of this application, we are only beginning our final year of research, which is primarily devoted to Aim #4, and we therefore fully expect to achieve the same level of excellent progress in Aim #4 as has been thus far achieved in the other aims.

Aim #1: Automatic determination of LV orientation from SPECT imagery: Correctly determining the orientation of the LV is important, since knowing this orientation allows the SPECT data can be "resliced" (i.e., viewed in 2D slices). If the data set is not properly oriented, the slices can be skewed and this can lead to possibly incorrect diagnoses. This task is completely finished. A robust, automatic, and consistently accurate method has been developed to determine the orientation or pose of the LV myocardial mass from SPECT imagery. This represents a significant intellectual contribution, since 3D pose determination is a long-standing problem in computer vision. Our innovative approach, which employs vision, image processing, and computer graphics methods to define an axis of orientation, has been generalized to problems dealing with other types of 3D data sets. A number of publications report on this method and its clinical evaluation [Ezq96a, Ezq96c, Kle93, Mul92, Mul94a], and a Ph. D. dissertation has also resulted from this work [Mul94b]. In addition, the resulting algorithm (DISHAT) is currently being implemented in General Electric Medical System's SPECT systems. We thus consider this task as having come to closure in a very positive manner. Appendix B.1 is also in [Mul92].

Aim #2 Knowledge Base modifications, extensions, and refinements: As previously mentioned, the construction of a visual reasoning model with which to interpret cardiac imagery has been at the core of our research throughout this program. Thus, a major thrust of our efforts has been devoted to exploring mechanisms for reasoning and knowledge representation. Consequently, the task of modifying, extending, and refining a KB remains a central theme in our previous, current, and future work. In keeping with this philosophy, the accomplishments associated with Aim #2 are numerous and significant. It would be worthwhile to briefly summarize the methods we have investigated in interpreting imagery. Broadly speaking, the approach is two-fold: (i) through a knowledge-guided paradigm that attempts to capture and represent, in a computational model, the visual reasoning process of experts, and (ii) through the implementation of this model within an intuitive UI that supports queries and interactive manipulations. Knowledge representation is achieved through rule- and frame-based methods, and are combined with spatial, temporal and uncertainty reasoning models to display and interpret the 3D imagery and other relevant textual and numeric information. Significantly, the interpretation methods infer structural information (the coronary vasculature associated with perfusion defects) from functional information (perfusion imagery). The knowledge-guided approach is implemented as an object-oriented system. A reprint of a publication fully describing the approach appears in Appendix B.2. We note that the methods to be used in the proposed research for enhancing this approach (as described in Section D) are based to a great extent on the discussions that immediately follow, and thus reference will be made in that section (D) to these discussions. We also observe that the preprint of Appendix B.2 further complements the discussions that follow.

The rule- and frame-based knowledge representation efforts have resulted in the creation of a knowledge base for interpreting perfusion imagery, PERFEXT (for perfusion expert). Creation of this KB has involved three broad, intensive efforts over several years: (i) a careful systematic, analysis of several hundred (well over 700) patient studies, (ii) a knowledge-acquisition and UI design effort spanning several years and involving a team of several, highly experienced clinicians who are members of our research team, and (iii) a series of extensive validation and usability studies involving retrospective and prospective clinical trials at local and external research sites [Ber96, Bra95, Bra96, Coo94, Coo95, Ezq92a, Ezq92b, Ezq93, Ezq94, Ezq95a, Ezq95b, Ezq96a, Ezq96c, Gar94a, Gar94b, Gar95, Gar96, Fol96, Her92, Kra96, Mul92, Mul94a, Pei92, Van96a, Van96b, WWW]. This body of work can be underscored with several, salient milestones, as discussed subsequently.

One major extension to the KB has been completed, which called for extending PERFEX to include both Tl-201 to Tc-99m MIBI perfusion radiopharmaceuticals. To ensure the ultimate success of this project, a program (CEqualT, which stands for Cedars-Emory Quantitative Analysis) to quantify myocardial perfusion from SPECT studies was independently developed, implemented, and tested. CEqual is a database-driven approach to quantification that compares the myocardial perfusion distribution extracted from a patient to a data base of normals as defined from patients with a < 5% likelihood of having coronary artery disease [Van93]. The method was shown to accurately detect and localize coronary artery disease in a multicenter study of 161 patients from 7 sites [Van94]. Four additional normal data bases have been developed and implemented; these are: (i) a two- day sestamibi database [Fol95], (ii) a stress-rest Tl201 data base, (iii) a rest Tl/stress sestamibi dual isotope data base [Are93], and (iv) a stress-rest tetrofosmin data base. The relevance of the quantification program CEqual to this project is that CEqual generates files that are used as input to the knowledge base, and, in fact, the radionuclide being used is transparent to PERFEX, since CEqual adjusts the input file according to the normal data base and criteria for abnormality for that tracer without having to use different forms of knowledge or reasoning strategies for each tracer. This strategy has already been developed, implemented and tested for Tc99m sestamibi [Gar95][Gar96], Tl201 [Gar96][Kra96] and for dual isotope imaging [Van94]. Hence, extension of the KB to handle other imaging agents gives the interpretation system more generality and clinical usefulness.

Another important, technical accomplishment has been the integration of numerous modifications into the knowledge-based system in order to improve its accuracy and robustness. To this end, a project was designed by our biostatistician (Clark) to compare the system's interpretations with those of one of our experienced physicians (J. Ziffer), using 100 cases of patients who had undergone a Tl-201 myocardial perfusion stress/ redistribution study. The objective was to detect discrepancies between the two sets of interpretations and to appropriately modify the KB (rather than to evaluate the system's degree performance, although obviously this was part of the study). As a result of this study, the KB underwent a number of significant changes to improve the representation of uncertainty associated with the evidence for (or against) disease. In particular, it was observed that certain myocardial territories can be perfused by different arterial vessels, and consequently this caused ambiguity or ambivalence relative to the strength with which a disease hypothesis could be stated. Subsequent analyses suggested that (i) the number of perfusion defects, (ii) the shape, location, extent, and severity of each defect, and (iii) the relationships between different defects in terms of relative location, were instrumental in resolving these ambiguities (or, in some cases, in declaring certain defects as ambiguous, which were also unresolved by the human expert). From these findings, new schemes for representing this knowledge were introduced. The resulting modifications were later evaluated with 288 patient cases, and further validated with the results of angiographic catheterization, as explained later in the discussions on testing and validation efforts.

An additional, major contribution toward enhancing the robustness of the KB consists of the identification of numerous clinical variables that should be taken into account in the overall decision-making process. The important aspect of this accomplishment is that most of the information that has been identified and integrated represents non-visual information. Thus, the knowledge-guided approach takes into account image as well as non-image, patient-specific information in the interpretation process. Two major projects in this area have been the identification and implementation of new forms of knowledge representation dealing with the use of additional clinical information (not used to date), and the design of a file format and an appropriate UI to access databases that contain this information.

The enhancements include representing knowledge to account for information regarding EKG results, attenuation artifacts due to large chest size, chamber size, lung uptake, etc. Specifically, the modifications include: (1) a refined description of the location of attenuation in terms of (i) anterior, inferior, and lateral walls for females, and (ii) anterior and inferior walls for males; (2) representation of the certainty of disease or ischemia based on the presence/absence of patient motion during stress, and the certainty of ischemia based on the presence/absence of patient motion at rest; (3) representation of the technical quality of the rest and stress studies; (4) representation of lung uptake information; (5) representation of the presence of transient ischemic dilatation (TID); (6) representation of the presence of hypertension; and representation of the presence of left bundle-branch block (LBBB). These, and other, types of patient-specific information are listed in Figure ZZ of Appendix ZZ1. We continue to implement other similar extensions, and expect to continue this type of robustness-enhancing modifications in the proposed research. Additionally, these enhancements have led to considering ways through which to mine the cardiac data bank and directly extract the relevant information through an intelligent database design, as proposed in Project #3.

Aim #3: Prediction of perfusion reversibility using artificial neural networks: As observed in Section B, the use of myocardial thickening information in conjunction with stress perfusion information can serve as a measure of the redistribution of perfusion in viable (but infarcted) myocardial tissue. In fact, if resting myocardial thickening is measured simultaneous to assessing myocardial stress perfusion distribution (dose injected at peak stress but imaged at rest), then determination of ischemia, scar and viable myocardium in a single setting would be possible [Gal83, Gal84, Zif91]. The clinical importance of this finding is significant, since aspects such as time, cost and morbidity could be considerably reduced. Unfortunately, the patterns of the rate of thickening, as well as the interpretation of the thickening and stress information together, represent a relatively new and complex interpretation problem. To address these considerations, machine learning methods have been explored to assist in the analysis, processing, and interpretation of this complex information. In particular, artificial neural networks have been investigated to predict redistribution information with thickening and stress information as input, as discussed next. We note that the methods to be used in the proposed research for reversibility prediction (described in Section D) are based to a great extent on the discussions that immediately follow, and thus reference will be made in that section (D) to these discussions. We also observe that the preprint of Appendix B.3 further complements the discussions that follow.

We previously reported that we had encountered an unexpected degree of difficulty in these investigations. The nature of the difficulty was the inconsistency between ANN training and testing results: a number of connectionist architectures were attempted which showed excellent convergence and performance during training but which yielded relatively poor results during testing. During the past year, there has been a technical breakthrough. One of the graduate students involved in the research, Eyal Schwartz (who obtained his M.S. degree in June 1995), discovered that the inputs to the ANNs were improperly defined, and reformulated the problem using unprocessed ("raw" image) input information and different network topologies. The resulting ANN has been successfully trained and tested such that perfusion reversibility can be consistently predicted, as further described below.

After Eyal's important contribution, several configurations of input data, output data and ANN topology have been examined. The data used in these studies consist of thickening and perfusion studies of 109 real patient cases, using Tc-99m sestamibi. For the purposes of training and testing the ANN, it was experimentally determined that partitioning the data into regions associated with individual perfusion defects (rather than associating a data set with each patient case) yielded optimal results. Thus, the input data sets were represented as sets of perfusion defects, where each defect consists of a closed region with reduced stress perfusion levels equal to or exceeding 2.5 standard deviations from normal levels [Ezq93]. This resulted in a data set containing 211 test cases, with one case for each defect. Of these 211 cases, 80 percent were randomly selected for training purposes, with the remaining 20 percent left for testing. Consistency and reliability of the study were improved by repeating each ANN training and test cycle 4 additional times, each time using another 20 percent of the complete data set for testing purposes. This approach has the result that, for each network topology, five different networks are being trained and tested. The results of testing the five networks are used to calculate the overall performance for all 211 cases, without violating the requirement that test cases are not allowed to be part of the training data set.

The ANN topology that has yielded optimal training and testing results thus far has the following configuration. The input layer consists of 64 nodes, made up of 32 values to describe each of the thickening and stress perfusion images. Each set of 32 values is derived from image information represented in polar format, as was illustrated in Figure 1. The polar maps are sampled into 8 angular regions and 4 regions describing the distance from the apical center, giving rise to the 32 regions encompassing the perfusion and thickening information. Figure 3 shows a polar image of stress perfusion (3a), and a similar polar image providing thickening information (3b), where both are subdivided into 8x4 polar representations. These images provide 32 descriptors each, yielding an input with a total of 64 values. The specific numerical input values are 32 standard deviations from normal (for perfusion) and 32 percentage values (for thickening). Prior to processing, these input values are first truncated to span a limited range (between 0 and 8 standard deviations for stress perfusion images, and between -325% and 600% for thickening percentages), and subsequently scaled between -1 and 1 to normalize the range of values. This preprocessing is needed because there is a large difference in value ranges between stress perfusion standard deviations and thickening percentages, and the ANN requires similar value ranges as inputs for proper behavior. Outside of a defect area, the stress perfusion input is set to -1.0.

The topology is a fully connected, feed-forward, back-propagation network with two hidden layers of 10 and 3 nodes. A standard sigmoid transfer function and delta learning rule were used. The output consists of one single node, providing a value indicating the average redistribution perfusion associated with the defect area in question. A bias connected to all processing elements of hidden and output layers is used to check if the input and output are scaled sufficiently to let the network focus the calculations on relating the changes in input and output to network weights (instead of improperly allocating resources to scale the values, which could also introduce inaccuracies). The test values for the output have been truncated between 0 and 5 standard deviations, and are then scaled between the values of 0.2 and 0.8, representing a limitation in possible output values for a backpropagation network in which a sigmoid transfer function is used. This ANN has been successfully trained, using 100,000 cycles. Each case of 80/20 percent training on an SGI indigo (100Mhz, R4000, 80MB internal) workstation requires approximately 25 minutes. An example of how the ANN analyzes the input information that enables the creation of a redistribution image is shown in Figure 3(b), using data from an actual patient case. The ANN provides one value as output, indicating the reversibility for the defect area. This single value is then substituted in the original polar image as a reversed area if the value exceeds a threshold of 0.30, a value determined by experimentation.

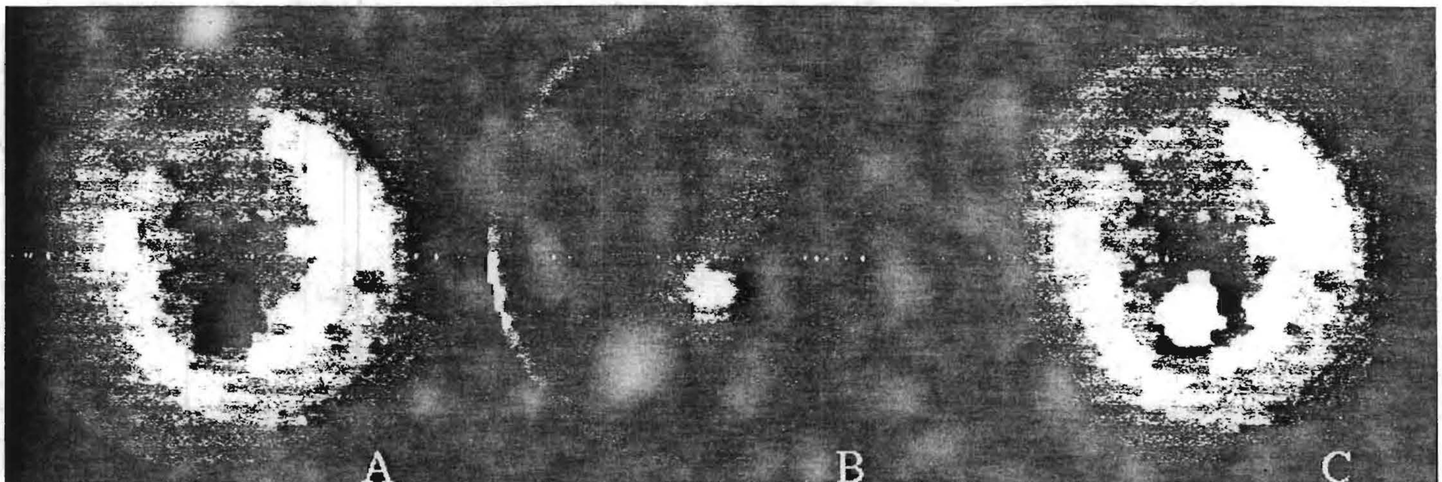

FIGURE 3. Input images (A) stress perfusion and (B) thickening, and (C) redistribution predicted by ANN.

The results obtained experimentally in predicting the occurrence of reversibility using the ANN-based method described above, based on tests conducted with the 109 patient data set, yield an overall accuracy of 72%. These preliminary results amply demonstrate the viability of the approach. These methods and associated results have formed the basis of a journal paper, which is included as Appendix B.3. At present, different and more complex data configurations and ANN topologies are being explored. Current research thrusts center on improving the predictive performance in terms of accuracy, reliability, and the ability to make reversibility predictions with greater quantitative granularity. These investigations form the basis for Aim #1 of the current application.

Aim #4: Knowledge extraction and integration of symbolic-connectionist methods: The main objective in this task is to extract knowledge from trained ANNs, and to subsequently fuse these connectionist methods with symbolic knowledge representation techniques. We observe that we are now beginning the third year of our research program, and the subsequent discussions represent partial yet extremely promising results that have thus far been achieved in this task. We note that the methods to be used in the proposed research (described in Section D) are based to a great extent on the discussions that immediately follow, and thus reference will be made in that section (D) to these discussions. We also observe that the preprint of Appendix B.4 further complements the discussions that follow.

We have conducted an extensive evaluation of current methods designed to interrelate symbolic and connectionist approaches. In particular, we explored various approaches for inserting knowledge into connectionist architectures and for creating hybrid connectionist-symbolic systems. The KBANN approach [Tow94] creates knowledge-based artificial neural networks by producing neural networks whose topological structure matches the dependency structure of the rules in an approximately-correct "domain theory " (collection of inference rules about the current task). Gallant and collaborators [Gal88] report on a connectionist expert system that simply utilizes a hand crafted modified backpropagation network that, once trained, can be used as an expert system. We view this approach as a specific hand-set implementation which KBANN is capable of producing. Another hybrid system, RuleNet, was reported in [McM92], which learns explicit symbolic condition- action rules in a formal string manipulation domain. RuleNet task description is similar to that of Cobweb [Fis87] based systems: inducing rules for classifying inputs based on a training example set in a symbolic oriented domain. Although this approach utilizes neural network techniques in the symbolic domain, we found this approach to be too restricted to specific type of problems. In addition, we found that too many of the initial hand crafted requirements makes this approach too limited for our purposes. Furthermore, our knowledge-based system, PERFEX, is already an extremely robust and consistently accurate system. Because of these limitations, we discarded knowledge-insertion approaches.

Regarding knowledge extraction, we examined various approaches for creating new rule dependency structures based on the final ANN connectivity. There appear to be two broad philosophies: direct and indirect knowledge extraction. In the direct approach, as described in KBANN method and its variations [Cra94, Opt93, Opt94, Tow93, Tow94, Gal88, McM92, Fis87], the algorithm traverses the network weights directly, performing grouping, pruning and other evaluation procedures in order to determine how output nodes depend on their predecessors. In the indirect approach, as described in the validity-interval analysis (VIA) [Thr93], a set of interval activation patterns are propagated through the trained network forward and backward where at each iteration the propagated intervals are compared to older intervals. Based on our analysis, Thrun's VIA approach was found to be the most interesting both in treatment and potential for future utilization. We have already successfully implemented this approach and have begun conducting preliminary validation and evaluation efforts. These preliminary results form the basis for the work detailed in section D.

Aim #5: System testing, validation, and refinement: A number of evaluation tests of the system have been conducted. One series of tests consisted of usability tests, designed to determine the ease-of-use and overall utility of the system as judged by several experts, while the other series of tests emphasized overall system performance in terms of providing accuracy, reliability, and robustness in a clinical setting. We note that similar usability testing and evaluation experiments will be used in the proposed research described in Section D, and thus the discussions that immediately follow will be referred to in that section (D). We also observe that the preprint of Appendixes B.5 and B.6 further complements the discussions that follow.

Usability Tests: Usability tests are an integral part of the UI design process, and the results of these tests are used to not only evaluate the system but also to further improve it. These tests involved usage and evaluation of various versions of the system by users having varying degrees of expertise in interpreting myocardial perfusion studies. Criteria used to evaluate the system included learning time, performance speed, user error rate, retention, and subjective satisfaction, based on well established HCI and Human Factors principles and methods [Bra95, Fol90, Loh90, Mar93, Shn87]. Four separate types of usability tests have thus far been performed.

The first type of usability test focussed on designing and improving an automatically generated report written in simple English (for clinicians). Specifically, tests were conducted to determine the most user-intuitive translation of the system's numerical outputs into a verbal (textual) patient study report. Users (Garcia, Krawczynska, Vansant) were asked to interpret a patient study and subsequently read a report generated for that specific case. They were then asked to formulate critiques on the generated report, both in terms of medical assessment and their own subjective linguistic preferences. Additionally, users were questioned regarding the way they perceived the generated report. In each iterative step, these critiques and answers were used to further improve numerical-to-textual translations of information, and were also useful in gaining insight in possible improvements of the knowledge base. This type of test was repeated several times iteratively, leading to the translation method currently used.

The second type of usability test was aimed at iteratively designing, implementing, and improving the mechanism for providing intuitive queries, justifications, and explanations. The same users that assisted in testing the report generator also participated in this test. At the beginning of each test, users were presented a patient case and a complete printout of possible justifications and explanations (without using PERFEX). In subsequent tests, users interacted with the interpretation system. In each case, users were asked to provide critiques and answers to questions based on their expertise and subjective linguistic preferences. Iterative improvements were thus made for the justification and explanation generator.

The third type of usability test was a complete test of the prototype system with the assistance of users with different levels of expertise. The users were asked to perform four or five interpretations of actual clinical cases using the graphical user interface (GUI), and were also asked to continuously supply remarks about what they were doing and why. This test was held in the Usability Testing Laboratory (at Georgia Tech), which is especially designed and well suited for this type of usability test. All of the sessions were videotaped for later, detailed analysis. The results of these tests led to the discovery of a series of ease-of-use limitations of the GUI. These limitations were carefully analyzed and formulated into a set of corresponding GUI enhancements. These enhancements are currently being either further investigated, refined, or implemented. Collectively, these usability tests have helped to create an interpretation environment that is highly useful, usable, and intuitive, as might be expected from an iterative design process that underscores user-centered, task-oriented, reduced-workload principles and methods. The final, fourth type of usability test was conducted externally at Cedars Sinai Medical Center in Los Angeles. The evaluation was extremely useful, as it pointed out a number of possible improvements which we, as original developers, had overlooked. Overall, however, the conclusion was reached that the interface was exceptionally useful and well designed, and that navigation through the image and information spaces was very easy. The details of the UI evaluation report are contained in Appendix B.6 [Ber96]. We are encouraged by these results, and plan to continue the iterative testing-and-refinement process.

Performance Tests: An important assessment of the interpretation system is the quantitative measurement of the system's accuracy, reliability, and robustness. Following the suggestions of the previous reviewers, we have conducted comparisons between the system and human experts, between the system and catheterization (cath) results, as well as evaluations conducted externally at another medical site. The first extensive validation consisted of 100 patients who had undergone a Tl-201 myocardial perfusion stress/redistribution study, a coronary angiography study and expert interpretation by one of our physicians (J. Ziffer). The objective was to detect and correct discrepancies between how the expert and PERFEX interpreted the scans. Through comparison of case-by-case discrepancies, it was concluded that in 39 of these patients the discrepancies were due to the human expert using variables external to the imaging study that at this point were not part of PERFEX. This analysis contributed to defining the additional variables needed by PERFEX that are described under Aim #1.

The 61 remaining Tl-201 patients (27 with cath correlation) were used to locate discrepancies between the human expert and the PERFEX knowledge base that could be corrected without introducing additional (non-image) variables. This evaluation and its results are described in detail in [Kra95]. In general, the results showed an excellent agreement between PERFEX and the human expert for detecting the presence (93%) and localizing CAD to the left anterior descending (LAD) artery (96%); left circumflex (LCX) artery (96%); and right coronary artery (RCA) (79%). The results were good, but less impressive for detecting the absence of CAD (61%) overall or in the vascular territories: LAD (58%), LCX (58%) and RCA (84%). These disagreements were concluded to be due mostly to the inherent limitation of not taking into account all of the clinical variables, as well as potential errors in interpretation by the human expert. The latter is addressed later by comparing to coronary angiographic results. Although this anatomic test is not expected to always agree with perfusion tests, it is still the accepted "gold standard" for detection and localization of CAD.

The previous validation was done with patients processed using the Emory polar display (Bull's-eye) approach to quantification [DeP85]. As explained earlier, a new quantification program (CEqual) was developed, validated and distributed for quantifying myocardial perfusion distributions, in particular Tc-99m sestamibi and Tl-201. The new CEqual program, CEqual output, and PERFEX input, were initially validated in detail in a group of seven sestamibi patients. The validation showed that these programs are performing as designed. Sixty prospective Tc-99m sestamibi patients (30 with cath correlation and 30 without, including 40 patients with CAD and 20 normals) were then used to validate the clinical efficacy of the CEqual/PERFEX program for detecting and localizing CAD. The results of this validation were presented at the American Heart Meeting in Anaheim [Gar95]. The results showed excellent agreement between PERFEX and the human expert for detecting the presence (95%) and localizing CAD to the LAD (92%), LCX (100%) and RCA (96%) vascular territories. As before, the results were good, but less impressive for detecting the absence of CAD (50%) overall or in the vascular territories: LAD (46%), LCX (71%) and RCA (76%). Remarkably, these results from a prospective population were quite similar to those from the Tl-201 test population used to iteratively modify the knowledge base. The full details and records of this evaluation are contained in Appendix B.5

The purpose of the next study [Gar96] was to validate PERFEX using a large prospective validation consisting of 150 stress/delayed Tl-201 and 138 rest/stress Tc-99m sestamibi myocardial perfusion studies in patients who also underwent coronary angiography catheterization (cath). The Tl-201 prospective group was comprised of 113 CAD patients and 37 normals, 103 were males and 47 females. The Tc-99m group was comprised of 90 CAD patients and 48 normals, 81 were males and 57 females. The visual interpretations (V) of slices and maps, vessel stenosis from coronary angiography (C) and PERFEX (Px) interpretations were all accessed automatically from data bases and used to automatically generate inter comparisons as shown in the table below. Results are (in %):

	Tl-201=	V vs C	Px vs C	Px vs V	**Tc-99m=**	V vs C	Px vs C	Px vs V
CAD	Sensitivity	91	89	90		86	87	95
	Specificity	22	30	56		23	10	46
LAD	Sensitivity	77	81	86		75	77	89
	Specificity	48	27	33		57	35	50
LCX	Sensitivity	58	67	86		57	69	95
	Specificity	89	53	51		85	47	47
RCA	Sensitivity	78	76	78		63	75	93
	Specificity	71	53	51		78	45	52

This study showed that PERFEX demonstrated a higher sensitivity and correspondingly a lower specificity than visual interpretation by human experts for identifying the presence and location of CAD. It also showed that the level of agreement between PERFEX and the human expert was better than that relative to coronary angiography.

An automatic comparison was made of cath, visual and PERFEX interpretations. The analysis for this project was done by automatically reading the results of the cath and visual interpretation from a local copy of the cardiac databank database. The results from PERFEX were automatically read from a "results" file that is stored on disk when PERFEX is run. For calculating sensitivity, specificity and accuracy, the cath results were considered the gold standard when comparing the visual interpretation with that of PERFEX. For comparing visual interpretation with PERFEX, the visual interpretation was considered the gold standard. Although this validation was performed in a prospective manner, this automated comparison provides a valuable tool to determine in just a few minutes how the behavior (robustness and accuracy) of PERFEX would change if any modification is made to the knowledge base or to any parameters used by the KB.

It would be instructive to describe the determination of CAD from each report. The cath and visual reports are derived from the output from the cardiac databank. The PERFEX report is derived from the patient file <xray #>.acr, which is output from "perfexj", the justification version of PERFEX (i.e., a version which provides tracing and justifications to the user regarding a particular interpretation conclusion). For all vessels, the maximum percent stenosis for the vessel is reported (i.e., the LAD % stenosis is equal to the maximum % stenosis of the entire LAD, each of the diagonals, and the septal perforator). For any vessel, if the stenosis is greater than or equal to 50%, then the vessel is considered to be diseased. For any vessel, if there is severe diffuse disease (indicated by a 50 % stenosis), then the vessel is considered to be diseased. If there is a left main stenosis greater than or equal to 50%, then both the LAD and the LCX are considered to be diseased. The D1 stenosis % is included in the LAD territory, so it does not need to be considered separately.

For visual determination of CAD, a number of corresponding guidelines were followed. For any vessel, a notation of "yes" or "probable" indicates the presence of disease in that vessel. A notation of "questionable" was counted both ways (the analysis was run twice, once meaning no disease, and once meaning disease). Only a notation of "no" indicates the absence of disease. The "OR" territories (equivocal pairs of vessels) are read giving the benefit to the reader, and could be interpreted as "either or both" of two vessels (i.e., LAD_or_LCX can be (i) LAD, (ii) LCX, or (iii) LAD and LCX). In those instances where there is no cath-documented disease in either of the OR territories (i.e., % stenosis < 50%), but there is visual evidence of disease in the OR territories, then one false-positive will be assigned to the vessel that has the higher % stenosis. In the case that both vessels have the same % stenosis, or both are 0, one false-positive will be assigned to one of the territories according to the following table, which is based on evidence of the location of the majority of false-positives gathered from many false-positive scans:

	LAD or LCX		RCA or LCX		LAD or RCA	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
FALSE-POSITIVE TERRITORY	LCX	LCX	RCA	LCX	RCA	LAD

Next, we describe PERFEX-based determination of CAD. For any vessel, a CF value greater than or equal to 0.2 in the diseased column indicates the presence of disease in that vessel. The "OR" territories are read giving the benefit to the reader, and could be interpreted as either or both (i.e., LAD_or_LCX = (i) LAD, (ii) LCX, or (iii) LAD and LCX). If there is no cath-documented disease, but disease concluded by PERFEX, then false- positives will be assigned according to the visual readings, as described above. We then performed a study to ascertain at what level of expertise PERFEX was performing [Kra96]. The study used a data-base of Tl-201 SPECT studies from 25 preselected patients who had undergone coronary arteriography. Over the last 10 years, these studies have been read independently by 6 faculty expert readers, 9 nuclear medicine residents with 12 months experience, 24 nuclear medicine residents with 3-6 months experience and 7 cardiology fellows. The results showed that although there appeared to be a trend towards higher specificity for the more experienced readers, statistical comparison of the sensitivity and specificity between groups of human experts did not reveal significant differences for any of the four diagnoses. Comparison between the human experts and PERFEX indicated no significant differences in sensitivity or specificity for CAD or RCA. However, the human experts had significantly lower sensitivity and correspondingly higher specificity than PERFEX for both LAD and LCX.

As requested by the study section who reviewed this proposal in 1993, an external validation was performed using data and interpretations from investigators other than those who helped develop PERFEX. As stated in our previous proposal, Dr. Daniel Berman and Kenneth Van Train from Cedars-Sinai Medical Center in Los Angeles acted as consultants on this study (at no cost to the project). At their laboratory, the routine is to use a Tl-201 rest/ Tc-99m sestamibi stress myocardial perfusion protocol. Modifications were made to CEqual's output program to generate a file consistent with the dual isotope normal data base and criteria for abnormality that could be interpreted by PERFEX. The procedure for this evaluation and the specific recommendations on a patient-by-patient basis are described in detail in the Appendix B.6 [Ber96]. In general, some specific recommendations were made by these investigators regarding how to improve the terminology used to indicate the names of the myocardial walls and how to modify some of the rules for increase specificity.

D. RESEARCH DESIGN AND METHODS

The knowledge-guided interpretation approach will be designed as an object-oriented computational model whose architecture is shown in Figure 4. The architecture schematically illustrated in Figure 4 provides an indication of the system's overall computational flow, and also serves as a guide to the discussions that follow. The control mechanism oversees all internal operations of the system, executes information-retrieval processes, and support user-system interactions.

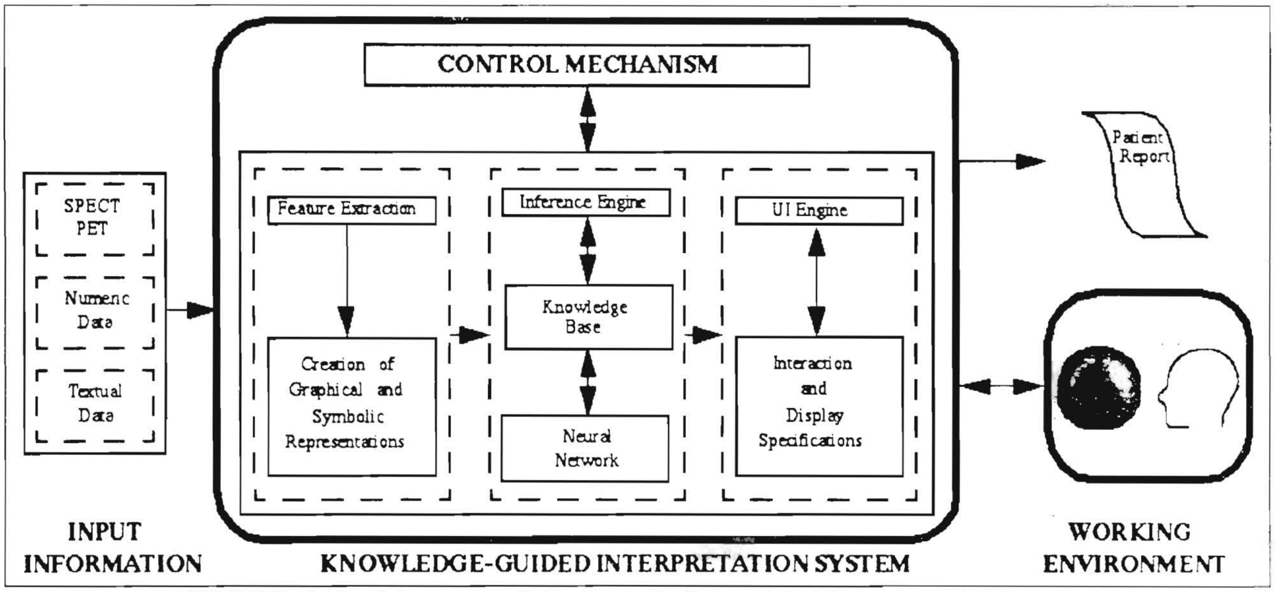

FIGURE 4. Architecture of the knowledge-guided interpretation system.

D. 1 Aim #1: Creation of a knowledge-guided SPECT interpretation model: This project consists of six sub-projects to (a) insure robustness and accuracy by extending the current knowledge-guided model to include all the necessary non-image information; (b) integrate uncertainty, temporal, probabilistic, and heuristic reasoning models, emphasizing the calculation of a priori likelihood of disease; (c) explore ANN techniques to predict perfusion reversibility and extract new knowledge; (d) design a UI to support these methods and functionalities; and (e) conduct extensive evaluations with large, prospective, well- characterized populations using both internal data, performing multicenter trials, and undertaking usability tests.

The core of the knowledge-guided approach is a computational model that attempts to capture and represent the visual reasoning process of experts. Knowledge representation is achieved through rule- and frame-based methods, and are combined with spatial, temporal and uncertainty reasoning models to display and interpret the 3D imagery and other relevant textual and numeric information, as described in below. The image information is pre-processed as described in Section C and in [Coo90] and [Ezq93], to extract both symbolic and graphical representations. The graphical representations include polar maps of standard deviation (SD), black-out (BO), and reversibility (RV) information, while the symbolic representations are a set of 32 description sectors ("descriptors") associated with four regions of myocardial depth (basal, medial, proximal apical and distal apical) and myocardial walls (septal, anterior, inferior, and lateral regions, as well as their pair-wise combinations). This mapping of the original image information into graphical and symbolic descriptors supports all subsequent knowledge-based processing. Although this preprocessing has been extensively documented before [Coo90, Ezq89, Ezq93, Gar90, Mul95] and continues to be part of the system shown in Figure 4, some preprocessing details are repeated in Section C and the preprint in Appendix B.2. Thus, the subsequent discussions assume the information has been pre-processed and already exists in terms of these graphical and symbolic representations, and no new pre-processing methods are proposed.

(a) Inclusion of all pertinent, non-image, clinical variables: This sub-project is a continuation of current work and will be performed during the first year of research. The results of our prior clinical evaluations clearly show that the main limitation of the current KB, PERFEX, is its reduced specificity for detecting and localizing CAD. From our case-by-case analysis, we have carefully documented that the main cause of this reduced specificity is

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A. SPECIFIC AIMS

The overall objective of this application is to develop a clinically useful, computer-based methodology to aid in the diagnosis of heart disease. The emphasis is placed on designing, implementing, and testing a methodology for (i) "mining" clinical databases (DBs) to discover possible associations and interdependencies that may be imbedded in the databases and which can improve diagnostic decision-making, (ii) using the resulting knowledge to create a robust knowledge base (KB) with which to interpret image and other relevant information, and (iii) placing the validated KB in the context of Internet-based communications to provide widespread access to this knowledge.

More specifically, the focus will be placed on designing and implementing novel DB mining algorithms with both local and remote DBs to uncover possible associations that may either confirm existing knowledge, refine existing knowledge, or lead to new knowledge regarding the detection and localization of coronary artery disease (CAD). The newly discovered (and validated) knowledge will subsequently be used to enrich a knowledge base that has been under development by our group to interpret both SPECT (single-photon emission computed tomography) image information, which is used in assessing myocardial (heart muscle) perfusion (blood flow), as well as other relevant, non-image patient-specific clinical information of a textual and/or numeric nature. These research activities will gradually be placed in the framework of distributed environments with a two-fold purpose: (a) to allow geographically dispersed users to consult the resulting KB remotely, and (b) to mine clinical DBs residing at several external, collaborating medical centers.

The general hypothesis underlying our research is that the resulting KB will provide an improvement in the accuracy of detection, localization and characterization (reversible vs. fixed perfusion defects) of CAD as interpreted from myocardial perfusion SPECT studies. This general hypothesis will be articulated in the form of more specific, testable hypotheses that consider performance comparisons between the knowledge-based approach, human experts, and coronary arteriography results. With this in mind, the specific aims are:

Aim #1: Knowledge Discovery: To design, implement and validate DB mining algorithms. These algorithms will mine both image and non-image (textual and numerical) databases to uncover possible knowledge (patterns, inferences, associations and their corresponding degrees of occurrence) relating the data to the diagnosis of hypoperfusion and coronary artery disease.

There are two tasks associated with this aim: (1.1) development of an architecture and data structure to support DB mining in both local and distributed environments; (1.2) continuation of ongoing, preliminary efforts to develop algorithms for (i) negative-rule and (ii) incremental DB mining, as well as association rules for (iii) sequence and (iv) quantitative data; and (v) analysis of algorithm efficiency.

Aim #2: Knowledge Base Enrichment: To represent the associations, inferences and corresponding degrees of certainty discovered through the DB mining efforts in terms of rules and statistically-based relationships, such that these rules and concomitant probabilistic support can be incorporated into the current KB.

This aim subsumes four tasks: (2.1) Formulation of rules resulting from DB mining: (a) verification and evaluation of (existing) knowledge (i.e., knowledge confirmation), and (b) evaluation of new (discovered) knowledge, distinguishing between knowledge that is new to the existing KB, new to the human experts, or new to both; (2.2) Creation of justifications (i.e., explanatory clauses) for the new (validated) knowledge; (2.3) Formulation of a probabilistically based representation of uncertainty from DB mining results; and (2.4) Extensive, multi-center testing and evaluation of the resulting KB at five external medical centers.

Aim #3: Distributed Knowledge Discovery and Knowledge-Based Processing: To extend the knowledge-based processing and knowledge-discovery methods such that (i) users can access the KB remotely and (ii) remote DBs can be accessed and mined (using proper security and authorization mechanisms).

There are three tasks related to this aim: (3.1) Design of an intuitive user interface that supports KB consultation, interactive 3D visualization, and query operations; (3.2) Development or adaptation of algorithms for distributed DB mining and knowledge-based processing; and (3.3) Continuation of multicenter testing and evaluation efforts.

The proposed research builds on our previous work on knowledge-guided image interpretation (see for instance, http://www.cc.gatech.edu/gvu/biovis/perfex/). These research activities represent an interinstitutional and interdisciplinary effort between Georgia Tech and Emory University, a strong collaboration that has yielded valuable insights, supported several academic degrees, and has resulted in numerous joint publications.

B. BACKGROUND AND SIGNIFICANCE

B.1 OVERVIEW

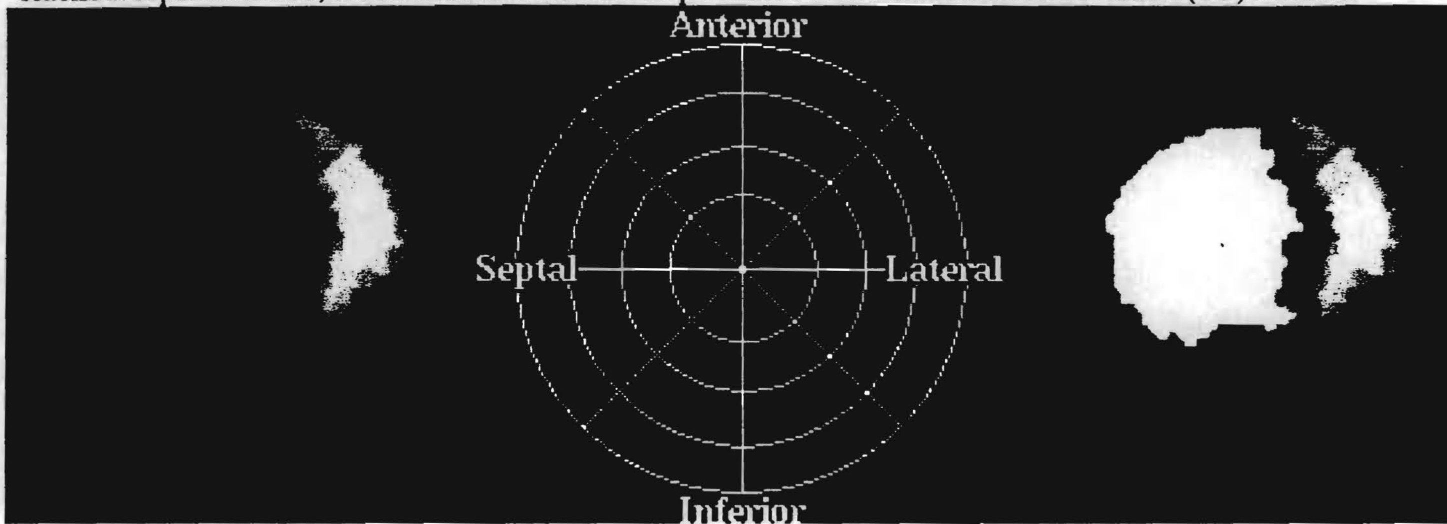
It is well recognized that heart disease has always been, and remains, a central health care problem. As observed by Pasternak, Braunwald and Sobel, "Heart disease continues to be the number one killer in the U.S., with 25% of all deaths related to coronary artery disease" [Pas92]. Furthermore, heart disease seriously affects the lives of millions: there are 1.5 million myocardial infarctions in the U.S. per year [Pas92, Kit88]. This deadly disease is not only costly in terms of irreplaceable human life, but also represents a significant economic factor in terms of staggering health care costs and overall loss of productivity. As a consequence of these considerations, the process associated with the prevention, detection, and treatment of heart disease remains one of the greatest concerns in all of health care. This process, in turn, relies on the careful acquisition, interpretation, and communication of ever increasing amounts of medical and clinical information.

It would appear that such an important and information-intensive process should benefit from emerging computer- and information-based technologies, as these technologies are, in fact, designed to process large amounts of information accurately, reliably, and efficiently. Importantly, recent interrelated developments in the fields of database design, distributed computing, artificial intelligence (AI), and human-computer interaction (HCI) suggest the emergence of extremely powerful and potentially significant mechanisms for extracting, representing, exploiting, and interacting with information derived from complex datasets. It is in this broad context that the present application seeks to make a contribution: through the exploration of frontier computing methods aimed at supporting and facilitating the decision-making process associated with assessing heart disease. In particular, we propose to design innovative techniques for extracting potentially new knowledge from clinical databases, use this knowledge to interpret the relevant medical information, and place the validated results in the context of Internet-based communications.

B.2 CARDIOVASCULAR IMAGING: RELEVANCE AND CHALLENGES

Clinical decisions regarding heart disease depend on the accurate and reliable assessment of coronary artery disease. In particular, decisions concerning a patient's diagnosis, therapy and prognosis are based primarily on two factors : (a) the extent and severity of atheromatous obstruction (i.e., a blockage or stenotic lesion in blood vessels) and (b) the degree of functional impairment caused by diseased myocardium (heart muscle) [Bru73a, Bru73b, Das77, Har79, Har80, Hum74, Lea81, Moc82, Rin83, Rou83a, Rou83b]. The "gold" standard for assessing the extent and severity of atheromatous obstruction is coronary angiography (X-rays of coronary arteries enhanced by a contrast medium) [Gou86], a standard that we will employ in our evaluation methods. On the other hand, tomographic perfusion (blood flow) imaging of the left ventricular (LV) myocardium, particularly SPECT imaging, is used as the "gold standard" in predicting not only blood flow to a myocardial region but also the amount of normal myocardium versus jeopardized but viable (ischemic) or infarcted (dead) myocardium, and remains the most widely accepted and preferred non-invasive imaging technique for assessing myocardial perfusion characteristics [DeP89]. Hence, myocardial SPECT imaging is an essential and routinely used process in assessing CAD. Currently, approximately three million patients per year are studied using myocardial perfusion studies in the United States, of which it is estimated that 80% use SPECT [DeP95]. The objective of this research is precisely to facilitate and support the interpretation of myocardial imagery and its integration with other clinical information represented.

Figure 1 shows a typical set of perfusion studies for an individual patient. The images on the left and right side (a and c) in this figure are polar representations of the three-dimensional (3D) myocardial perfusion information, extending from the apical region (center of the polar map) through the basal region (outermost circumference of the polar map) of the heart. The polar maps (also called "Bull's Eye" plots) are processed, quantified, and color coded using a color table that maps those areas containing relatively high concentrations of radioactive tracer (i.e., higher perfusion levels) into bright colors (e.g., yellow and orange), while those areas that contain relatively low tracer concentrations when compared to "normal" patient populations (and thus represent regions of hypoperfusion, or perfusion "defects") are mapped into darker colors (e.g., magenta and blue) [Coo90, DeP88]. In Figure 1, the image in (a) corresponds to a "stress" (ST) tomographic acquisition, obtained immediately after the patient has exercised. Figure 1(b) shows the polar map subdivided into 32 myocardial regions. Typically, another tomographic acquisition is obtained hours after exercise while the patient is at rest, resulting in a "delayed" (DL) image (not shown). The image in 1(c) corresponds to reversibility (RV), which is the normalized difference between the delayed and stress distributions. Stress images are useful in determining perfusion defects in general (and infarctions in particular), while delayed and reversibility images are useful in determining possible perfusion redistribution (i.e., ischemia, indicating viable myocardium). It is important to note that the image in 1(a) is a "blackout" (BO) image, wherein regions beyond a predetermined number of standard deviations below the mean normal distribution are set to a pixel value of zero. The BO stress image of Figure 1(a) thus indicates a severely hypoperfused region (the region in black). In addition to the blackout representation, the information can also be presented in raw and standard deviation (SD) formats.



(a) (b) (c)

Perfusion imaging: (a) a perfusion image taken at peak stress displayed in polar format, (b) a division of the polar map into 32 regions, and (c) a delayed perfusion image.

Figure 1 appropriately suggests that well established techniques are available to routinely display and quantify myocardial perfusion, thereby providing a mechanism for expressing the location, extent, and severity of perfusion defects and perfusion defect reversibility. [DeP88, DeP89, Coo90, DeP95]. In terms of the foregoing discussions, the goal is thus to utilize all this image information (raw, BO, SD representations of the ST, DL and RV distributions) to accomplish the task of diagnostic interpretation. This, of course, can easily become a challenging visual and cognitive task. It is possible to learn to interpret this information by visually interpreting the imagery. However, this requires extensive training and experience. We will briefly mention how the proposed research will address these and other challenges.

Interpretation of Diverse Types of Information. One of the principal challenges is the required mental integration of the visual information with other relevant, clinical data (such as patient symptoms and electrocardiographic results). This difficulty is compounded by the fact that SPECT image information is essentially functional information (i.e., it provides a measure of myocardial perfusion distribution), and yet the diagnostic decision normally requires the physician to infer structural information from these images (particular the coronary vessels associated with hypoperfusion defects). Hence, structure must be inferred from function. These challenges call for new ways of integrating and interpreting these complex sets of diverse - yet possibly interrelated- sources of information in a consistently accurate and reliable manner. With this in mind, Aim#1 is devoted to the development, implementation and testing of data mining techniques aimed at uncovering patterns and associations that may be present in imagery and related clinical variables.

Diagnostic Performance. Another important consideration is the efficiency with which diagnostic decisions are to be made: as the volumes of information multiply (and the health care environment evolves), clinicians are expected to interpret all of the information with the highest accuracy possible (avoiding incorrect interpretations) and in the shortest amounts of time possible. Diagnostic interpretation performance can be both supported and significantly improved by providing assistance to the user through reduced workload, task analysis considerations, and the use of domain knowledge. The basis for this hypothesis is an emerging body of knowledge showing that principles and methods of AI and HCI can be invoked to guide and facilitate this information-intensive, interpretive task [Man94, Kle89, San89a, McC87, Cle85, Tuf83, Mar93, Mas91, Shn87, Mac86, Cha73, Rot94, San89b, Ezq93]. This is further validated by evidence supporting the concept that computer quantification of myocardial perfusion images improves not only the overall diagnostic yield but also enhances reliability, accuracy, confidence and reproducibility of interpretation [Wac94]. In this regard, Aim#2, concentrates on confirming, refining, and/or extending our relatively robust knowledge base (PERFEX) by reformulating the findings resulting from the DB mining efforts in terms of specific rules of inference.

Reliability and Standardization. A further challenge affecting medical imaging in general is the lack of standardization and the related inter-observer and intra-observer variabilities. Standardization is difficult as the visual interpretation process involves complex interrelationships between the observer, the characteristics inherent in the information, and other factors such as task definition, level of expertise, and the interaction environment [Kle89, San89a, Cle85, Ras86, Tuf83, Mar93, Shn87]. Because of the wide variability in the training that physicians have in interpreting these studies [Cer94], there is a wide variability in the accuracy of how these studies are interpreted [Kra96]. It is recognized that diagnosticians with less expertise tend to fail to recognize imaging artifacts and clinical variables and interpret at lower levels of specificity [DeP89][Kra96]. It has also been pointed out that a trained observer can disagree with his or her own diagnostic interpretation (when presented with the same image information) as much as 15% of the time [Con82]. In addition, physicians with less experience in interpreting perfusion imagery may be required to make diagnostic decisions without the supervision of clinical experts. We consider these challenges in Aims #1 ,#2 and #3.

3D Visualization. Another consideration addressed in our research is the fact that the image information itself is generally displayed in formats that are not intuitive. As suggested in Figure 1, the images are commonly presented as a series of polar maps which are clearly distorted representations of 3D perfusion distributions, similarly to the way in which the Earth's true surface is distorted in a 2D Mercator projection. These considerations create a significant visual workload even for experienced physicians. The degree of difficulty associated with this demanding and ill-defined task is reflected in the observation that medical experts can sometimes prefer certain types of display formats over others, believing the selected formats to be optimal, despite the fact that tests of their own visual performance indicate otherwise [Gil89]. We will directly address these concerns in Aim #3 by creating an intuitive user interface (UI) and a 3D cardiovascular model [Fol90, Loh90, Mar93, Shn87].

Related Research As the foregoing discussions suggest, the clinical assessment of CAD may be viewed as a vital problem in health care and an information- and knowledge-intensive task that requires extensive experience, the integration of visual and non-visual data, and the extraction of inferences from information that is inherently complex and increasingly expanding. From the decision-making perspective, the task involves complex interrelationships between perceptual, cognitive, and human-computer interaction variables. As noted earlier, there is increasingly compelling evidence that principles and methods of artificial intelligence, scientific visualization, and human-computer interaction can be invoked to facilitate such information-intensive, interpretive tasks [Man94, Kle89, San89a, McC87, Cle85, Tuf83, Mar93, Shn87, Mac86, Cha73, Rot94, San89b, Ezq93]. The use of these principles, especially computer-based methods, can be traced back several decades [Sch38, Led59, Lip61, Gor73, Buc84, Pop81, Wei78, Pat81]. Since this body of knowledge is well known and well documented, we will limit the present discussions to a brief summary of recent work concerned with interpreting cardiac information, and contrast these methods to our approach.

Our methods for cardiac image interpretation are distinct from other approaches in a number of ways. In contrast to model-based methods which look at heart physiology and function by considering arrhythmias and ECG information [Wid92, Ton93], the proposed research considers this information while also taking into account image information directly. A number of investigators have researched the interpretation of cardiac imagery by (i) using methods based on artificial neural networks (ANNs) [Por94, Ham95, Fuj92], (ii) considering the intelligent processing of LV wall motion or some subset of the imagery [Dun84, Tso85], (iii) emphasizing a particular method of uncertainty reasoning [Ros86], or (iv) using rule-based [Rei87, Hor90, Nie85] or (v) case-based [Had95] models. There are several limitations associated with these approaches. One is that a single reasoning or knowledge representation method is used. Also, in the case of ANN-based approaches, it is difficult to infer new insights or knowledge from ANNs, while rule-based and case-based approaches suffer from knowledge-acquisition bottlenecks as well as KB or case-base incompleteness. Our approach, however, combines uncertainty, temporal, probabilistic and abductive reasoning approaches, thereby exploiting and integrating the respective strengths of these paradigms to create a more comprehensive visual reasoning model. Importantly, none of the image interpretation approaches reported in the literature have been extended to provide diagnostic support remotely, nor to mine knowledge from DBs.

B.3 DATABASE MINING

Database mining, also known as knowledge discovery, is defined as the automated discovery of previously unknown, nontrivial, and potentially useful information from databases. The information is a statement that describes the relationship among a set of objects contained in the database with a certain confidence such that the statement is in some sense simpler than enumerating all the relationships between the individual instances of objects [FPSM91]. For example, in a database of employees and their salaries, each instance represents the relationship between an individual employee and his salary. A statement such as ``salaries of engineers is higher than the salaries of secretaries," based on the instances of the database, conveys information that is implicit and more interesting than listing the salaries of all engineers and secretaries. Database mining is the process of generating high-level patterns that have acceptable certainty and are also interesting from a database of facts. A more detailed, technical description of DB mining is given in Section C.2 (Preliminary Studies), while a brief report, which can be viewed as a brief, self-contained tutorial on DB mining, is provided in Appendix B.

Foundational Principles and Potential Traditionally, DB systems have supported a type of inference called *deduction* which infers information that is a logical consequence of the information in the database [Ull88]. However, in database mining we are interested in another type of inference called induction that is generalized from the database [Mic83]. In other words, database mining infers information that is *supported* by the database as opposed to *categorically correct* statements with respect to the database [HS93a]. DB mining also involves detecting statistically significant regularities. Knowledge discovery derives much of its success from reasoning techniques in artificial intelligence, expert systems, machine learning and statistics. Many paradigms such as inductive learning [Qui86], Bayesian statistics [HSC90], rough sets [Paw94], mathematical taxonomy [DE82], and conceptual clustering [ANB92] have also been applied to knowledge discovery. In general, knowledge discovery is an amalgamation of concepts from diverse fields. Knowledge discovery has in fact been applied effectively to solve many diverse problems. Examples include discovering rules of mass spectrometry from spectrogram data [BM78], assessment of credit card applicants [CC87], discovering rules for query optimization [SSS91, SHKC93], inferring risk profiles of insurance policy holders [Sie94], and general business applications [KI91, SSU91, SAD+93, Tsu90]. Due to its generalizability and potential, database mining has thus developed into an important area of research in database systems in the past few years. The number of publications in recent conferences on databases also supports this observation [vld94, vld95, SW94, YC95]. We can attribute this at least in part to the tremendous growth in available data in the past few years. Widespread use of computers and low cost storage systems have resulted in huge amounts of data being collected routinely, as has certainly been the case in medical imaging. With the present rate of increase in the volume of data, it is obvious that manually analyzing this data will soon be impossible. Clearly, sophisticated analysis systems are necessary to extract information hidden in such databases. Also, inferring valuable high-level information based on large volumes of routine data is becoming critical for making sound decisions. As a result, database mining has the potential to address, and is motivated by, decision support problems faced by most organizations and is thus perceived as an important area of research [SSU91, SAD+93]. This potential regarding the extraction of valuable "hidden" information from large DBs can be brought to bear in the medical domain.

Technical Issues One of the main challenges in database mining is developing fast and efficient algorithms that can discover associations in large volumes of data, and the corresponding association rules. Discovering association rules was introduced in [AIS93], and have been discussed in the literature for discovering association rules in a database of customer transactions [AIS93, AS94, HS93b, SON95]. However, these algorithms have not in general been applied to either the medical domain or to imaging problems. There are a number of other important technical issues related to DB mining. These include the concepts of certainty (relative statistical significance), quality (degree to which contents of the DB are accurately reflected), representation (the forms used to represent the extracted information), usefulness (criteria for assessing how valuable the information is in a particular problem or domain), autonomy (degree to which DB mining algorithm is guided or supervised), and efficiency (size of DBs to which algorithm can be applied). In Section C, we describe the DB mining algorithm used in our current studies to address these issues, while Section D presents a formal problem description and algorithms for incremental and sequential knowledge discovery.

Medical Knowledge Discovery DB mining methods have only recently been introduced in the medical domain [MYGS91]. Consequently, the field of medical knowledge discovery is largely unexplored, despite the fact that its impact can be significant for a number of reasons. First, the real or anticipated pressure from managed care companies to request documentation regarding the proper utilization of diagnostic procedures is generating a trend for many clinical sites to create, maintain, and interpret increasingly large DBs. Second, clinical DBs have a wealth of information (particularly when combined from multiple sites) which could be used to support diagnostic and therapeutic decisions. Third, in the context of medical imaging, the information is vast and inherently complex, and must be analyzed in the context of other, related information. DB mining algorithms consequently provide a mechanism for more efficiently organizing, accessing, and interpreting the clinical information. In this regard, our proposed efforts can serve as a model for mining medical DBs in general, and medical imagebases in particular. Coupled with the notion of a multicenter DB setting, the results of the proposed research have the potential of being both pioneering and extremely useful.

B.4 DISTRIBUTED KNOWLEDGE DISCOVERY & KB PROCESSING

The explosive emergence of telecommunications capabilities presents both an opportunity, and in some sense an obligation, to place medical imaging research in a relevant, forward-looking context. At the root of this telecommunications explosion is the Internet in general, and the World Wide Web (WWW, or "Web") in particular. We quote from a special report that recently appeared in Science [Sci96] regarding the impact (and promise) of these technologies relative to medical informatics and bioinformatics: "The Internet was born in December of 1969 and has grown phenomenally since. Its graphically attractive, user-friendly modality, the WWW, is younger and grown even more explosively. By its nature, the WWW is a tool ideally and uniquely suited for the advancement of [medical] education." In the same report, the following is also noted: "Bioinformatics and the Internet are...two of computer science's boom areas."

Clearly, the informational landscape is changing in a truly profound way, and medical informatics research activities should plan accordingly. In the proposed research, there are a number of ways in which we plan to benefit from, and contribute to, these informational trends and opportunities. In particular, we will explore both knowledge discovery and knowledge-based image interpretation in distributed environments. The knowledge discovery currently being investigated, and further developed in Aim #1, will be reformulated in Aim #3 in the context of mining several remote clinical DBs. As detailed in the Methods Section D, five medical centers will collaborate in this project to create a multi-center, distributed "global" database. Consequently, we will create incremental and sequential DB mining algorithms to take advantage of a potentially "continuously" growing amount of clinical information with which to enhance our knowledge regarding the assessment of CAD. In addition, we will investigate other related issues, such as a Web-based interface to support data entry, and security and record confidentiality issues. Thus, this task will likely lead to basic contributions, insights and tools regarding distributed medical DB mining. We expect that these five collaborating centers will represent only an initial set of remote DB sites, and that additional centers will be included as the research program progresses. The motivation for participating is four-fold: the opportunity to collaborate in frontier medical research, the benefit derived from mining the centers' own DBs, the benefit derived from enhancing diagnostic knowledge, and the use of the resulting KB.

Regarding distributed image interpretation, we feel that the results of our research can serve as a model for providing Internet-based expert knowledge for general diagnostic medical imaging. As outlined in Aim #3, the knowledge base will be made available to any physician and/or facility world-wide for decision support through electronic access. This is significant not only from the viewpoint of providing decision support on-line to virtually any person or organization linked to the distributed architecture, but also because this task (i) contributes to, and benefits from, the aforementioned telecommunications initiatives, (ii) relates to trends in health care management and cost-containment, (iii) raises the possibility of continuous KB confirmation, discovery, and enhancement, and (iv) promotes the concept of patient-centered care in the future, wherein the patient him/herself can perhaps access his/her own medical information. In addition to exploring distributed knowledge-based image interpretation methods, we will also create (as part of Aim #3) a highly interactive user interface capable of providing query support (to explain or clarify conclusions and interpretations), and interactive visualization of patient imagery, other clinical information, and a 3D cardiac model (using JAVA-based techniques and emerging programming concepts to support program execution and graphical manipulation).

C. PROGRESS REPORT AND PRELIMINARY STUDIES

This section contains three major portions: (i) a progress report summarizing our previous achievements (Section C.1), (ii) a summary of the publications and personnel involved in the project (Section C.2), and (iii) a discussion of our recent, ongoing research activities and preliminary results related to DB mining (Section C.3).

C.1 PROGRESS REPORT

The present report covers the three-year period 02/01/94 through 01/31/97. The URLs for different Web sites associated with prior research results are also given in the report.

Specific Aims The objective of the research has been to develop computer-based methods to assist in the diagnosis of heart disease. In particular, the thrust of the research has been to develop methods for assisting in the diagnostic interpretation of cardiovascular 3D imagery. The specific aims for the project period were: (1) Automatically determine the orientation of the left-ventricular (LV) myocardium from SPECT imagery (such that the data set is properly aligned relative to the natural LV axis); (2) Modify and extend a previously created KB to interpret the imagery (to increase robustness and accuracy); (3) Predict perfusion reversibility using ANNs (such that only one image acquisition is necessary); (4) Extract knowledge from trained ANNs (integrating connectionist and symbolic (rule-based) methods); and (5) Test, validate and enhance the system's accuracy, robustness, and usability.

Overview of Progress Prior to discussing the specific achievements associated with these aims, we observe that in our opinion these research aims have largely been met. Specifically, Aim #1 (orientation determination) was completely finished (and resulted in a Ph.D. degree thesis), while Aim #2 (KB refinement) resulted in a significantly enhanced KB whose performance was amply demonstrated in evaluations (in Aim #5) and which similarly provided the basis for a post graduate thesis. Our efforts toward Aim #3 yielded valuable insights regarding reversibility prediction using artificial neural networks. Aim #4 (knowledge extraction from ANNs) proved to be challenging, as the results were somewhat limited by the number of patient cases for which both the required stress and thickening information was available. Due to these data set limitations, coupled with the relatively complex nature (and size) of the images, and the demanding data requirements associated with ANN training, it was felt that the extraction of knowledge from ANNs presented a statistically limited (though intellectually sound) experiment. Aim #5 (evaluation, which was integrated into each of the other four aims) was actually a continuous process of testing and evaluation to systematically test and refine our approach. The evaluation efforts were conducted both by our institutions as well as by another center (Cedars Sinai Medical Center, Los Angeles, CA) and demonstrated the accuracy and reliability of our knowledge-based image interpretation method.

Summary of Accomplishments and Significance of Findings: The results thus far obtained are of both clinical and scientific value: (1) a method for automatically determining the orientation of a 3D object (LV myocardial mass) imbedded in a 3D data set (SPECT imagery) has been created, and has subsequently been generalized to other medical and non-medical domains, thereby representing a solution to a general problem in computer vision; (2) the knowledge-guided methods resulting from our research can aid in interpreting cardiac imagery in a consistently accurate and reliable manner, thereby facilitating this information-intensive task; (3) the approach has been shown to be generalizable to different perfusion agents, giving the approach greater clinical usefulness; (4) the approach also infers structural information (coronary vessels involved) from functional information (myocardial perfusion); (5) a user interface (UI) has been designed, implemented, and evaluated, which provides users with timely, intuitive, and practical support within the normal clinical environment, and which provides justifications and explanations in a highly dynamic manner; (6) the interpretation methods integrate both stress and delayed (reversibility) information; (7) the entire process, from image acquisition through interpretation, has been almost completely automated, resulting in a valuable and practical clinical tool; (8) a highly innovative method has emerged with which to predict one type of image (reversibility distribution) from other input images (stress perfusion distribution and percent thickening) through ANNs; and (9) extensive tests and evaluation experiments have been conducted both internally and externally to demonstrate the performance of the resulting KB. These accomplishments have served as the basis for a number of publications (listed later in this section), and are elaborated further below.

Aim #1: Automatic determination of LV orientation from SPECT imagery: Correctly determining the orientation of the LV is important, since knowing this orientation allows the SPECT data to be "resliced" (i.e., viewed in 2D slices). If the data set is not properly oriented, the slices can be skewed and this can lead to possibly incorrect diagnoses. This task is completely finished. A robust, automatic, and consistently accurate method has been developed to determine the orientation or pose of the LV myocardial mass from SPECT imagery. This represents a significant intellectual contribution, since 3D pose determination is a long-standing problem in computer vision. Our innovative approach, which employs vision, image processing, and computer graphics methods to define an axis of orientation, has been generalized to problems dealing with other types of 3D data sets. A number of publications report on this method and its clinical evaluation [Ezq96a, Ezq96c, Kle93, Mul92, Mul94a], and a Ph. D. dissertation has also resulted from this work [Mul94b]. In addition, the resulting algorithm (DISHA) is currently being implemented in commercial SPECT imaging systems. We thus consider this task as having come to closure in a very positive manner. Appendix A contains representative publications (the project results can be visualized by visiting the http://www.cc.gatech.edu/gvu/biovis/perfex/).

Aim #2 Knowledge Base modifications, extensions, and refinements: The approach we have investigated in interpreting imagery can be broadly viewed as two-fold: (i) formulation of a knowledge-guided method that attempts to capture and represent, in a computational model, the visual reasoning process of experts, and (ii) implementation of this model within an intuitive UI that supports queries and interactive manipulations. Knowledge representation is achieved through rule- and frame-based methods, and are combined with spatial, temporal and uncertainty reasoning models to display and interpret the 3D imagery and other relevant textual and numeric information. Significantly, the interpretation methods infer structural information (the coronary vasculature associated with perfusion defects) from functional information (perfusion imagery). The knowledge-guided approach is implemented as an object-oriented system, resulting in PERFEX (for "perfusion expert"). Creation of this KB has involved three broad, intensive efforts over several years: (i) a careful systematic, analysis of over 1,000 patient studies, (ii) a knowledge-acquisition and UI design effort spanning several years and involving a team of several highly experienced clinicians who are members of our research team, and (iii) a series of extensive validation and usability studies involving retrospective and prospective clinical trials at local and external research sites.

One major extension to the KB has been completed, which called for extending PERFEX to include both Tl-201 to Tc-99m MIBI perfusion radiopharmaceuticals. To ensure the ultimate success of this project, a program (CEqual, which stands for Cedars-Emory Quantitative Analysis) to quantify myocardial perfusion from SPECT studies was independently developed, implemented, and tested. [Van94]. The relevance of the quantification program CEqual to this project is that CEqual generates files that are used as input to the knowledge base, and, in fact, the radionuclide being used is transparent to PERFEX, since CEqual adjusts the input file according to the normal data base and criteria for abnormality for that tracer without having to use different forms of knowledge or reasoning strategies for each tracer. This strategy has already been developed, implemented and tested for Tc99m sestamibi [Gar95, Gar96], Tl201 [Gar96, Kra96] and for dual isotope imaging [Van94]. Hence, extension of the KB to handle other imaging agents gives the interpretation system more generality and clinical usefulness. An additional, major contribution toward enhancing the robustness of the KB consists of the identification of numerous clinical variables that should be taken into account in the overall decision-making process. The important aspect of this accomplishment is that most of the information that has been identified and integrated represents non-visual information. Thus, the knowledge-guided approach takes into account image as well as non-image, patient-specific information in the interpretation process. The enhancements include representing knowledge to account for relevant information including: (1) a refined description of the location of attenuation in terms of (i) anterior, inferior, and lateral walls for females, and (ii) anterior and inferior walls for males; (2) representation of the certainty of disease or ischemia based on the presence/absence of patient motion during stress, and the certainty of ischemia based on the presence/absence of patient motion at rest; (3) representation of the technical quality of the rest and stress studies; (4) representation of lung uptake information; (5) representation of the presence of transient ischemic dilatation (TID); (6) representation of the presence of hypertension; and representation of the presence of left bundle-branch block (LBBB). Importantly, these clinical variables are at the basis of the DB mining algorithms proposed in the current application.

Aim #3: Prediction of perfusion reversibility using artificial neural networks: The use of myocardial thickening information in conjunction with stress perfusion information can serve as a measure of the redistribution of perfusion in viable (but infarcted) myocardial tissue. In fact, if resting myocardial thickening is measured simultaneous to assessing myocardial stress perfusion distribution (dose injected at peak stress but imaged at rest), then determination of ischemia, scar and viable myocardium in a single setting would be possible [Gal83, Gal84, Zif91]. The clinical importance of this finding is noteworthy, since aspects such as time, cost and morbidity could be considerably reduced. Unfortunately, the patterns of the rate of thickening, as well as the interpretation of the thickening and stress information together, represent a relatively new and complex interpretation problem. To address these considerations, machine learning methods were explored to assist in the analysis, processing, and interpretation of the information. In particular, artificial neural networks have been investigated to predict redistribution information with thickening and stress information as input.

Several configurations of input data, output data and ANN topology were examined. The data used in these studies consist of thickening and perfusion studies of 109 real patient cases, using Tc-99m sestamibi. For the purposes of training and testing the ANN, it was experimentally determined that partitioning the data into regions associated with individual perfusion defects (rather than associating a data set with each patient case) yielded optimal results. Thus, the input data sets were represented as sets of perfusion defects, where each defect consists of a closed region with reduced stress perfusion levels equal to or exceeding 2.5 standard deviations from normal levels [Ezq93]. This resulted in a data set containing 211 test cases, with one case for each defect. Of these 211 cases, 80 percent were randomly selected for training purposes, with the remaining 20 percent left for testing. Consistency and reliability of the study were improved by repeating each ANN training and test cycle 4 additional times, each time using another 20 percent of the complete data set for testing purposes. This approach has the result that, for each network topology, five different networks are being trained and tested. The results of testing the five networks are used to calculate the overall performance for all 211 cases, without violating the requirement that test cases are not allowed to be part of the training data set. The topology is a fully connected, feed-forward, back-propagation network with two hidden layers of 10 and 3 nodes. A standard sigmoid transfer function and delta learning rule were used. This ANN has been successfully trained, using 100,000 cycles. Each case of 80/20 percent training on an SGI indigo (100Mhz, R4000, 80MB internal) workstation requires approximately 25 minutes. The ANN provides one value as output, indicating the reversibility for the defect area. This single value is then substituted in the original polar image as a reversed area if the value exceeds a threshold of 0.30, a value determined by experimentation. The results obtained experimentally in predicting the occurrence of reversibility using the ANN-based method described above, based on tests conducted with the 109 patient data set, yield an overall accuracy of 72%. These preliminary results amply demonstrate the viability of the approach. These methods and associated results have formed the basis of publications [deB96, deB96b, Ezq92b, Paz92] as well as a Masters thesis project.

Aim #4: Knowledge extraction and integration of symbolic-connectionist methods: The main objective of this task was to extract knowledge from trained ANNs, and to subsequently fuse these connectionist methods with symbolic knowledge representation techniques. We have conducted an extensive evaluation of current methods designed to interrelate symbolic and connectionist approaches. In particular, we explored various approaches for inserting knowledge into connectionist architectures and for creating hybrid connectionist-symbolic systems. The KBANN approach [Tow94] creates knowledge-based artificial neural networks by producing neural networks whose topological structure matches the dependency structure of the rules in an approximately-correct "domain theory " (collection of inference rules about the current task). Gallant and collaborators [Gal88] report on a connectionist expert system that simply utilizes a hand crafted modified backpropagation network that, once trained, can be used as an expert system. We view this approach as a specific hand-set implementation which KBANN is capable of producing. Another hybrid system, RuleNet, was reported in [McM92], which learns explicit symbolic condition-action rules in a formal string manipulation domain. RuleNet task description is similar to that of Cobweb [Fis87] based systems: inducing rules for classifying inputs based on a training example set in a symbolic oriented domain. Although this approach utilizes neural network techniques in the symbolic domain, we found this approach to be restricted to specific types of problems. Because of these limitations, we discarded knowledge-insertion approaches. We also explored knowledge extraction, and examined various approaches for creating new rule dependency structures based on the final ANN connectivity [Cra94, Opt93, Opt94, Tow93, Tow94, Gal88, McM92, Fis87]. Based on our analysis, Thrun's VIA approach [Thr93] was found to be the most interesting both computationally and in terms of its potential for future utilization. We successfully implemented this approach and conducted preliminary validation and evaluation efforts. We have also investigated various methods for fusing symbolic and connectionist approaches [Gal88, McM92, Fis87].

Despite this progress, however, research on connectionist approaches will not be continued. As observed in the review of our resubmission, "the suitability of the proposed artificial neural network approach is uncertain." We concur with this observation and have revised our plans accordingly. Despite the fact that our efforts have led to interesting and promising results, these efforts have been somewhat limited by the number of patient cases for which both the required stress and thickening information was available. Due to these data set limitations, coupled to the relatively complex nature (and size) of the images, and the demanding data requirements associated with ANN training, it was felt that the extraction of knowledge from ANNs presented a statistically limited (though intellectually sound) experiment. As a result of these considerations, and spurred by the observation made by the reviewers, we have concluded to pursue neither the prediction of myocardial reversibility using ANNs nor the extraction of knowledge from the associated (trained) ANNs. It should be observed, however, that several publications resulted from this research, providing insights regarding the prediction of images using ANNs.

Aim #5: System testing, validation, and refinement: Two different sets of evaluation experiments were conducted. One series of tests emphasized overall system performance in terms of providing accuracy, reliability, and robustness in a clinical setting; this set actually consisted of five different evaluation experiments. The other set of tests consisted of usability tests, designed to determine the ease-of-use and overall utility of the system as judged by several experts. We note that similar usability testing and evaluation experiments will be used in the proposed research described in Section D, and thus the discussions that immediately follow will be referred to in that section (D).

Performance Tests: An important assessment of the interpretation system is the quantitative measurement of the system's accuracy, reliability, and robustness. Thus, we have conducted extensive evaluation experiments consisting of five types of tests: (1) comparisons between the system and an expert; (2) evaluation of both Tl-201 and Tc-99m sestamibi; (3) comparisons between the system and coronary angiography catheterization (cath) results; (4) comparisons between the knowledge-based system and several different human experts; and (5) evaluations conducted at an external site.

(1) Human-KB Comparisons: The first validation consisted of 100 patients who had undergone a Tl-201 myocardial perfusion stress/redistribution study, a coronary angiography study and expert interpretation by one of our physicians (J. Ziffer). The objective was to detect and correct discrepancies between how the expert and PERFEX interpreted the scans. Through comparison of case-by-case discrepancies, it was concluded that in 39 of these patients the discrepancies were due to the human expert using variables external to the imaging study that at this point were not part of PERFEX. This analysis contributed to defining the additional variables that will be used in DB mining, as described under Aim #1. The 61 remaining Tl-201 patients (27 with cath correlation) were used to locate discrepancies between the human expert and the PERFEX KB that could be corrected without introducing additional (non-image) variables. This evaluation and its results are described in detail in [Kra95]. In general, the results showed an excellent agreement between PERFEX and the human expert for detecting the presence (93%) and localizing CAD to the left anterior descending (LAD) artery (96%); left circumflex (LCX) artery (96%); and right coronary artery (RCA) (79%). The results were good, but less impressive for detecting the absence of CAD (61%) overall or in the vascular territories: LAD (58%), LCX (58%) and RCA (84%). These disagreements were concluded to be due mostly to the inherent limitation of not taking into account all of the clinical variables, as well as potential errors in interpretation by the human expert. The latter is addressed later by comparing to coronary angiographic results. Although this anatomic test is not expected to always agree with perfusion tests, it is still the accepted "gold standard" for detection and localization of CAD.

(2) The validation described in (1) above was done with patients processed using the Emory polar display (Bull's-eye) approach to quantification [DeP85]. As explained earlier, a new quantification program (CEqual) was developed, validated and distributed for quantifying myocardial perfusion distributions, in particular Tc-99m sestamibi and Tl-201. The new CEqual program, CEqual output, and PERFEX input, were initially validated in detail in a group of seven sestamibi patients. The validation showed that these programs are performing as designed. Sixty prospective Tc-99m sestamibi patients (30 with cath correlation and 30 without, including 40 patients with CAD and 20 normals) were then used to validate the clinical efficacy of the CEqual/PERFEX program for detecting and localizing CAD. The results of this validation were presented at the American Heart Meeting in Anaheim [Gar95]. The results showed excellent agreement between PERFEX and the human expert for detecting the presence (95%) and localizing CAD to the LAD (92%), LCX (100%) and RCA (96%) vascular territories. As before, the results were good, but less impressive for detecting the absence of CAD (50%) overall or in the vascular territories: LAD (46%), LCX (71%) and RCA (76%). Remarkably, these results from a prospective population were quite similar to those from the Tl-201 test population used to iteratively modify the

knowledge base. The full details and records of this evaluation are contained in Appendix C.

(3) The purpose of the next study [Gar96] was to validate the KB using a large prospective validation consisting of 150 stress/delayed Tl-201 and 138 rest/stress Tc-99m sestamibi myocardial perfusion studies in patients who also underwent coronary angiography catheterization (cath). The Tl-201 prospective group was comprised of 113 CAD patients and 37 normals, 103 were males and 47 females. The Tc-99m group was comprised of 90 CAD patients and 48 normals, 81 were males and 57 females. The table below summarizes the results, where V = visual interpretations of slices and maps, C = vessel stenosis from coronary angiography, and Px = PERFEX interpretations (and all results are in %):

		Tl-201			Tc-99m		
		V vs C	Px vs C	Px vs V	V vs C	Px vs C	Px vs V
CAD	Sensitivity	91	89	90	86	87	95
	Specificity	22	30	56	23	10	46
LAD	Sensitivity	77	81	88	75	77	90
	Specificity	48	27	43	57	35	60
LCX	Sensitivity	58	67	94	57	69	98
	Specificity	89	53	67	85	47	65
RCA	Sensitivity	78	76	86	63	75	95
	Specificity	71	53	69	78	45	61

This study showed that PERFEX demonstrated a higher sensitivity and correspondingly a lower specificity than visual interpretation by human experts for identifying the presence and location of CAD. It also showed that the level of agreement between PERFEX and the human expert was better than that relative to coronary angiography. The interpretation is that the specificity can be improved by including in the KB a number of additional clinical variables which are not currently considered in the KB [Kra96]. Hence, the proposed work will build on these results to further refine the KB and improve specificity by including these variables, as discussed in Section D.

(4) The next study used a database of Tl-201 SPECT studies from 25 preselected patients who had undergone coronary arteriography. Over the last 10 years, these studies have been read independently by 6 faculty expert readers, 9 nuclear medicine residents with 12 months experience, 24 nuclear medicine residents with 3-6 months experience and 7 cardiology fellows. The results showed that although there appeared to be a trend towards higher specificity for the more experienced readers, statistical comparison of the sensitivity and specificity between groups of human experts did not reveal significant differences for any of the four diagnoses. Comparison between the human experts and PERFEX indicated no significant differences in sensitivity or specificity for CAD or RCA. However, the human experts had significantly lower sensitivity and correspondingly higher specificity than PERFEX for both LAD and LCX. As noted earlier, we will continue to improve the KB by including a number of clinical variables in the knowledge-based processing.

(5) As requested by the study section who reviewed this proposal in 1993, an external validation was performed using data and interpretations from investigators other than those who helped develop PERFEX. As stated in our previous proposal, Dr. Daniel Berman and Kenneth Van Train from Cedars-Sinai Medical Center in Los Angeles acted as consultants on this study (at no cost to the project). At their laboratory, the routine is to use a Tl-201 rest/Tc-99m sestamibi stress myocardial perfusion protocol. Modifications were made to CEqual's output program to generate a file consistent with the dual isotope normal data base and criteria for abnormality that could be interpreted by PERFEX. The procedure for this evaluation and the specific recommendations on a patient-by-patient basis are described in detail in the Appendix C and [Ber96]. In general, the results were consistent with those of (1), (2), and (4) above, while some specific recommendations were also made by these investigators regarding how to improve the terminology used to indicate the names of the myocardial walls and how to modify some of the rules for increase specificity.

Usability Tests: Usability tests are an integral part of the UI design process, and the results of these tests are used to not only evaluate the system but also to further improve it. These tests involved usage and evaluation of various versions of the system by users having varying degrees of expertise in interpreting myocardial perfusion studies. As observed in the Introduction, usability testing is inherently an iterative design-test-redesign cycle which is not-trial and-error but consists of a series of scientific experiments based on well established HCI and Human Factors principles and methods [Bra95, Fol90, Loh90, Mar93, Shn87]. Criteria used to evaluate the system included learning time, performance speed, user error rate, retention, and subjective satisfaction. Four separate types of tests were performed, designed to evaluate the usability of: (1) Reporting mechanisms; (2) Mechanisms supporting queries and justifications; (3) a prototype UI design, tested locally (at Emory U.); and (4) a prototype UI design, tested externally at Cedars-Sinai. The details of the UI evaluation report are contained in Appendix C and in [Ber96]. We are encouraged by these evaluation results, and plan to continue extensive evaluation and usability testing using these methods, as discussed in Section D.

(1) The first type of usability test focussed on designing and improving an automatically generated report written in simple English (for clinicians). Specifically, tests were conducted to determine the most user-intuitive

translation of the system's numerical outputs into a verbal (textual) patient study report. Users (Garcia, Krawczynska, Vansant) were asked to interpret a patient study and subsequently read a report generated for that specific case. They were then asked to formulate critiques on the generated report, both in terms of medical assessment and their own subjective linguistic preferences. Additionally, users were questioned regarding the way they perceived the generated report. In each iterative step, these critiques and answers were used to further improve numerical-to-textual translations of information, and were also useful in gaining insight in possible improvements of the knowledge base. This type of test was repeated several times iteratively, leading to the translation method currently used.

(2) The second type of usability test was aimed at iteratively designing, implementing, and improving the mechanism for providing intuitive queries, justifications, and explanations. The same users that assisted in testing the report generator also participated in this test. At the beginning of each test, users were presented a patient case and a complete printout of possible justifications and explanations (without using PERFEX). In subsequent tests, users interacted with the interpretation system. In each case, users were asked to provide critiques and answers to questions based on their expertise and subjective linguistic preferences. Iterative improvements were thus made for the justification and explanation generator.

(3) The third type of usability test was a complete test of the prototype system with the assistance of users with different levels of expertise. The users were asked to perform four or five interpretations of actual clinical cases using the graphical user interface (GUI), and were also asked to continuously supply remarks about what they were doing and why. This test was held in the Usability Testing Laboratory at Georgia Tech (formally The Georgia Institute of Technology, or GIT), which is especially designed and well suited for this type of usability test. All of the sessions were videotaped for later, detailed analysis. The results of these tests led to the discovery of a series of ease-of-use limitations of the GUI. These limitations were carefully analyzed and formulated into a set of corresponding GUI enhancements. These enhancements are currently being either further investigated, refined, or implemented. Collectively, these usability tests have helped to create an interpretation environment that is highly useful, usable, and intuitive, as might be expected from an iterative design process that underscores user-centered, task-oriented, reduced-workload principles and methods.

(4) The final, fourth type of usability test was conducted externally at Cedars Sinai Medical Center in Los Angeles. The evaluation was extremely useful, as it pointed out a number of possible improvements which we, as original developers, had overlooked. Overall, however, the conclusion was reached that the interface was exceptionally useful and well designed, and that navigation through the information spaces was very easy.

C.2 PERSONNEL AND PUBLICATIONS

Personnel It is important to observe that this grant has supported several individuals who either have obtained, or are in the process of obtaining, advanced (graduate) degrees through their work on this research. One student (Rakesh Mullick), received a Ph.D. degree from GIT in August 1994; Rakesh's dissertation was in fact the subject of specific aim #1 (orientation determination). Two students received Master's degrees: Eyal Schwartz (M.S. June 1995, GIT), whose work was in ANNs (aim #3), and Levien de Braal (M.S. July 1994, Technical University of Delft, The Netherlands), whose user interface (UI) design and usability studies (aim #5) defined his thesis theme. In addition to the degrees granted to these individuals, three other graduate students have also significantly contributed to the project; two of these remain degree candidates in Georgia Tech's Ph.D. program (James O'Brien and Thomas Browne) while the third contributor (Joaquín Madrid) will earn his degree in Spain. It is also noteworthy that one of the aforementioned individuals, Levien de Braal, has been hired as a Research Scientist to continue his outstanding research work.

A total of twenty-five individuals have contributed directly to this project (Alazraki, Berman, Clark, Collum, Cooke, de Braal, DePuey, Ezquerra, Faber, Folks, Garcia, Herbst, Hise, Hyche, Krawczynska, Maojo, Martín, Mingo, Mullick, Pazos, Ríos, Robbins, Schwartz, Vansant, Van Train, Ziffer), as evidenced in their contributions to various publications. These individuals include senior investigators, students, as well as visiting scholars. Indeed, it is worthwhile noting that several scientists and post-doctoral fellows contributed to the research while visiting GIT from the Universidad Politécinca de Madrid (UPM), Madrid, Spain, under a GIT-UPM agreement. These investigators were: A. Pazos, M.D.-Ph.D. (1992); Víctor Maojo, M.D.-Ph.D. (1992); F. Martín, Ph.D. (1992); Prof. Juan Ríos, Ph.D. (1994), and Fernando Mingo, Ph.D. candidate (1996). The work (primarily related to Aims #2, #3 and #4) conducted by these visiting scientists came at no cost to the project, as they were funded by the Spanish government. Thus, the project not only benefitted from their contributions, but also served as a vehicle through which to enhance their careers.

Publications The findings and results associated with this research have contributed toward the body of knowledge in medical informatics, particularly in the areas of interpretation, visualization, and reasoning about medical imagery. It should be stressed that this publications list is not merely large (approximately 40 publications), but it is also of high quality and encompasses two important medical informatics communities: the community of computer scientists and engineers, and the community of medical scientists and clinical researchers. Software systems and electronic publications resulting from the research are also included below. Appendix A contains reprints of several of the papers. (The publications span a period beginning prior to 2/94.)

"Topological Goniometry: An Approach to Orientation Determination of Cylindrical Objects," N. Ezquerra and R. Mullick, ACM Transactions on Graphics, Vol. 15, No. 2, pp. 99-120, April (1996).

"Knowledge-Guided Visualization of 3D Medical Imagery" N. Ezquerra, L. de Braal, R. Mullick, D. Cooke, E. Krawczynska and E. Garcia; submitted to IEEE Trans. on Medical Imaging.

"Automatic Determination of LV Orientation from SPECT Data," R. Mullick and N. Ezquerra, IEEE Transactions on Medical Imaging, Vol. 14, No. 1, March 1995.

N. Ezquerra, R. Mullick, D. Cooke, E. Krawczynska, and E. Garcia,"PERFEX: An Expert System for Interpreting Perfusion Images," invited paper, Expert Syst. With Apps., Vol. 6, pp. 459-468, 1993.

"Advanced Computer Methods in Cardiac SPECT" (book chapter), C. D. Cooke, T. Faber, and E. V. Garcia, in Cardiac SPECT Imaging, E.G. DePuey, D.S. Berman, and E.V. Garcia, eds.; Raven Press, Ltd., New York, NY, pp. 75-89 (1995).

Inteligencia Artificial en Medicina, (Artificial Intelligence in Medicine, published in Spanish), with A. Pazos. ISBN 84-88051-42-5, Colección Informática No. 3-1994, Fund. A. Brañas, Pub.; Santiago de Compostela, Spain, 1994.

“Myocardial Ischemia Detection by Expert System Interpretation of Thallium-201 Scintigrams,” with M. Herbst, E. Garcia, D. Cooke, R. Folks, and G. DePuey; in Cardiovascular Nuclear Medicine and MRI, J. Reiber and E. Van der Wall, eds., Kluwer Academic Publishers (1992).

Expert System Interpretation of Myocardial Perfusion Tomograms: Enhancements and Validation," N. Ezquerra, E. Garcia, C.D. Cooke, E. Krawczynska, J. Vansant, L. de Braal, and R. Mullick; Circulation, Vol. 92, No. 8, #0048, 1996.

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“Expert System Interpretation of Myocardial Perfusion Tomograms: Validation Using 288 Prospective Patients,” with E. Garcia, E. Krawczynska, R. Folks, D. Cooke, J. Vansant, and N. Alazraki; J. Nuc. Med., Vol. 37, No. 5, p. 48P, 1996.

“Effect of Physician Training on Performance of Interpreting Cardiac Tl-201 SPECT Studies: Comparison to Expert System Results, with E. Krawczynska, N. P. Alazraki, W. S. Clark, C. D. Cooke, R. D. Folks, and E. Garcia; J. Nuc. Med., Vol. 37, No. 5, p. 179P, 1996.

“Expert System Interpretation of Technicium-99m Sestamibi Myocardial Perfusion Tomograms,”with E. Garcia, D. Cooke, E. Krawczynska, R. Folks, J. Vansant, L. de Braal, and R. Mullick, Circulation, Vol. 92, No. 8, I-10, October 1995.

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"Knowledge-Based Visualization of Myocardial Perfusion Tomographic Images," with E. V. Garcia, M. D. Herbst, C. D. Cooke, B. L. Evans, R. D. Folks, and E. G. DePuey; IEEE Proc. Visualization in Biomedical Computing (VBC '90), pp. 157-161. Conference, Atlanta, GA, May (1990).

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Software Systems and Electronic Publications

[WWW] World Wide Web entry: http://www.cc.gatech.edu/gvu/biovis/perfex/

"Visualization of Medical Imagery," ACM Special Interest group on Biomedical Computing (SIGBIO) CD-ROM, Vol. 14, NO. 3, September 1995.

DISHA™, an algorithm for determining the orientation of the myocardium (heart muscle) from 3D SPECT imagery. The software is based on the dissertation work of R. Mullick and has been implemented on General Electric Medical Systems scanners and is being licensed to GE. Software disclosure filed with GIT Office of Technology Licensing.

PERFEX™, an **ex**pert system for interpreting **per**fusion imagery. The software has been implemented on some imaging scanner manufacturers' systems, and is under clinical evaluation. Software disclosure is being filed with GIT's Office of Technology Licensing.

PERFUSE™, an interactive **use**r interface to support knowledge-based processing of **per**fusion images (see expert system PERFEX™ software cited above). Based on thesis work of L. de Braal; software disclosure has been filed with GIT's Office of Technology Licensing.

C.3 DATABASE MINING: PRELIMINARY STUDIES

Some of the basic concepts in DB mining were introduced earlier (in Section B.3), such as associations, rules, confidence, etc. In this section, we provide a formal description of these concepts and introduce our current algorithm. During our preliminary research in knowledge discovery, we have concentrated on creating algorithms for finding associations, rather than on optimization issues; the latter is discussed in Section D.

Problem Description This section is largely based on the description of the problem in [AIS93] and [AS94] (in the following, the original "transaction" is taken to be a clinical datapoint, either one of the 32 descriptor values in the image or a clinical variable associated with the patient, such as age, sex, or values of clinical tests.) Formally, the problem can be stated as follows: Let $I = \{i_1, i_2, ..., i_m\}$ be a set of m distinct literals called items. D is a set of variable length transactions over I. Each transaction contains a set of items $i_i, i_j, ..., i_k \subset I$. A transaction also has an associated unique identifier called *TID*. An ***association rule*** is an implication of the form $X \Rightarrow Y$, where X, $Y \subset I$, and $X \cap Y = \emptyset$. X is called the ***antecedent*** and Y is called the ***consequent*** of the rule. In this way, rules of inference are obtained.

In general, a set of items (such as the antecedent or the consequent of a rule) is called an *itemset*. The number of items in an itemset is called the *length* of an itemset. Itemsets of some length k are referred to as k--itemsets. For an itemset $X \cdot Y$, if Y is an m--itemset then Y is called an *m-extension* of X. Each itemset has an associated measure of statistical significance called ***support***. For an itemset $X \subset I$, $support(X) = s$, if the fraction of transactions in D containing X equals s. A rule has a measure of its strength called ***confidence*** defined as the ratio $support(X \cup Y) / support(X)$.

The problem of **mining** association rules is to generate all rules that have support and confidence greater than some user specified minimum support and minimum confidence thresholds, respectively. This problem can be decomposed into the following subproblems:

1. All itemsets that have support above the user specified minimum support are generated. These itemset are called the *large* itemsets. All others are said to be *small*.
2. For each large itemset, all the rules that have minimum confidence are generated as follows: for a large itemset X and any $Y \subset X$, if $support(X)/support(X - Y) \geq minimum\_confidence$, then the rule $X - Y \Rightarrow Y$ is a valid rule.

For example, let $T_1 = \{A,B,C\}$, $T_2 = \{A,B,D\}$, $T_3 = \{A,D,E\}$ and $T_4 = \{A,B,D\}$ be the only transactions in the database. Let the minimum support and minimum confidence be 0.5 and 0.8 respectively. Then the large itemsets are the following: $\{A\},\{B\},\{D\},\{AB\},\{AD\}$ and $\{ABD\}$. The valid rules are $B \Rightarrow A$ and $D \Rightarrow A$.. Discovering all large itemsets and their supports is a nontrivial problem if the cardinality of the set of items, $|I|$, and the database, D, are large. For example, if $|I| = m$. the number of possible distinct itemsets is 2^m. The problem is to identify which of these large number of itemsets has the minimum support for the given set of transactions. For very small values of m, it is possible to setup 2^m counters, one for each distinct itemset, and count the support for every itemset by scanning the database once. However, for many applications m can be more than 1,000. Clearly, this approach is impractical. It should be noted that only a very small fraction of this exponentially large number of itemsets will have minimum support. Hence, it is not necessary to test the support for every itemset. Even if practically feasible, testing support for every possible itemset results in much wasted effort. To reduce the combinatorial search space, all algorithms exploit the following property: any subset of a large itemset must also be large. For example, if a transaction contains itemset *ABCD*, then it also contains *A*, *AB*, *BC*, *ABC*, etc. Conversely, all extensions of a small itemset are also small. For example, if the itemset *ADE* is small, then none of the itemsets which are extensions of *ADE*, i.e., *ADEF*, *ADEFG*, etc., need be tested for minimum support. This property is used by all existing algorithms for mining association rules as follows: initially support for all itemsets of length 1 (1-itemsets) are tested by scanning the database. The itemsets that are found to be small are discarded. A set of 2-itemsets called *candidate itemsets* are generated by extending the large 1-itemsets generated in the previous pass by one (1-extensions) and their support is tested by scanning the database. Itemsets that are found to be large are again extended by one and their support is tested. This process is repeated until no more large itemsets are found. These fundamental concepts are the foundation of our algorithms.

Algorithm The algorithm we have used initially is based on the Apriori algorithm [AS94]. The algorithm is shown below. To generate the candidate itemsets for the algorithm we do the following: let L_{k-1} be the set of large *(k-1)*-itemsets, to discover the set L_k of candidate k-itemsets, we compute $L_{k-1} * L_{k-1}$, where * is a concatenation operation. The concatenation operation is defined formally, as $L_i * L_i = \{X \cup Y \mid X,Y \in L_i, \mid X \cap Y \mid = i\text{-}1\}$*.

procedure find_large_itemsets
$L_1 = \emptyset$;
generate candidate 1-itemsets, C_1, from the set of items in the database;
generate support for the candidate 1-itemsets by a pass over the database;
If the support for each item, c, in the candidate 1-itemsets . minimum support
    Then insert c in L_1
    Else discard c;
more_item_sets = *true*;
$k = 2$;
While *more_item_sets* Do
    Begin
        $L_k = \emptyset$;
        generate candidate k-itemsets, C_k
            by 1-extensions of the large *(k-1)*-itemsets, L_{k-1};
        generate support for the candidate k-itemsets by a pass over the database;
        If the support for each item, c, in the candidate k-itemsets . minimum support
            Then insert c in L_k
            Else discard c;
        If $L_k = \emptyset$ Then *more_item_sets* = *false*;
        $k = k + 1$;
    End;

Pseudocode: Procedure find_large_itemsets

The use of "support" in DB mining is one way to eliminate the generation of uninteresting associations of fields and hence uninteresting rules. A value for support that is too high restricts our algorithm from finding possibly interesting rules and a value too low produces many uninteresting rules that would have to be examined by the user. Neither is an optimal situation. Since the optimal support may be difficult to determine, we propose a new and novel approach that combines (i) data partitioning and (ii) domain knowledge along with support. The idea with data partitioning is that, once we find an association with the minimum support, we partition the data to just those records that contribute to the support for the association. For example, we might be interested in finding associations concerning a particular disease such as LAD stenosis. In the original set of records, there may be enough support for LAD stenosis but not enough support for that attribute in conjunction with others such as chest circumference. However, if we partition the data to just those records that support LAD stenosis and use the support with respect to that number of records, other interesting and valuable associations those patients can emerge. The idea of partitioning will also be expanded beyond just a single level, thereby introducing a partitioning tree structure. In addition, the use of domain knowledge such as "rule templates" can be used to avoid generating rules that do not fit the template. For example, we might look for associations/rules that involve a diagnosis as the consequent of the rule. This would be a rule template, where the consequent is fixed but the antecedent is not. The antecedent may be one or many attributes that are mined by our algorithm. In addition, the consequent in the rule template may be a subset of the mined consequent. Both of these techniques are being used to prune the search space as well as to help ensure that interesting associations/rules are discovered.

Input Data We ran our association algorithm on the patient data that included both image and textual information. The data consisted of 288 patient cases. The only image data considered for our preliminary work were stress images taken from the set of myocardial imagery data (we will consider delayed image information in our proposed work). Rather than using the entire range of image values we constrained our preliminary work to binary image values, and thus the preprocessed stress image was input as a 4 X 8 Boolean matrix. The textual data included fields such as *age, weight, sex, chest circumference, LAD, RCA,* and *Q-waves* information. Since our preliminary *association-finding* algorithm considers only binary data, an appropriate mapping of the non-binary valued fields into binary values was constructed. The program was written in C and is close to 1,000 lines of source code. The program was run on a Sun Sparc multiprocessor machine and took approximately 30 minutes CPU time. The minimum support needed to be considered an association was 25%.

Preliminary Results As an illustration of the types of results we have obtained in our preliminary studies, the following three rules have been inferred from DB mining:

IF ([InferoLateral] [Chest Circum])
THEN ([Normal Cath])
WITH support=33.3% AND confidence=100.0%

IF ([LaterInferior] [Chect Circum])
THEN ([Normal Cath])
WITH support=33.3% AND confidence=100.0%

IF ([LateroAnterior] [Chect Circum])
THEN ([Normal Cath])
WITH support=28.6% AND confidence=100.0%

These rules suggest that, of all patients sent to coronary angiography (cath) because of expected CAD, perhaps due to abnormal perfusion studies, about 33% of them had both large chest circumference (greater than 40 inches) and artifacts that appeared as perfusion abnormalities in the InferoLateral, LateroInferior and LateroAnterior contiguous myocardial walls. Thus we have learned that patients with a large chest circumference will create a photopenic artifact in these three contiguous segments. This is extremely useful and interesting from several aspects. First, new knowledge has emerged from the mining relating the information to the detection of CAD. Second, this knowledge was discovered from simultaneously considering image and non-image patient Dbs, demonstrating the usefulness of being able to interpret diverse types of complex information with mining algorithms - a task that would be time-consuming and challenging even to experts. Third, the discovered knowledge is statistically supported by the DB population in terms of both support and confidence factors. We have similarly uncovered many other new rules and associations in our preliminary studies, and will continue these knowledge discovery efforts through algorithm development for (i) incremental and (ii) negative-rule DB mining; as well as association rules in (iii) sequence and (iv) quantitative data; (v) algorithm efficiency optimization, and (vi) distributed DB mining.

D. RESEARCH DESIGN AND METHODS

This section describes the methods to be used in the research, and consists of three subsections dealing with: (D.1) Knowledge Discovery, (D.2) Knowledge Base Enrichment, and (D.3) Distributed Knowledge Discovery and Knowledge-Based Processing. The algorithms' computational designs, their implementation with imagebases, and their application to the medical domain, are fundamentally new contributions.

D.1 AIM #1: KNOWLEDGE DISCOVERY: The overall goal is to design, implement, and validate DB mining algorithms. These algorithms will mine both image and non-image (textual and numerical) databases to uncover possible knowledge (patterns, inferences, associations and their corresponding degrees of occurrence) relating the data to the diagnosis of hypoperfusion and coronary artery disease. At the outset, we observe that our knowledge discovery efforts will span the four-year period of research. (A schedule of the four-year program is given at the end of Section D.) This is because knowledge discovery represents both the overarching theme of the research as well as one of the major time-consuming efforts. In addition, the DB mining efforts will incrementally migrate from local to distributed, multicenter DBs.

<u>D.1.1 Development of Underlying Data Structures and Support Middleware</u> To conduct DB mining and knowledge-based processing in both local and distributed environments, it is necessary to first create an appropriate layer of supporting middleware and design the appropriate data structures. These issues are discussed subsequently in the context of an architecture whose schematic design appears in Figure 2 below. It is noted that this effort will continue throughout the four-year program in order to both extend the architecture to remote sites, as well as to integrate advances and emerging tools in Internet- and Web-based communications.

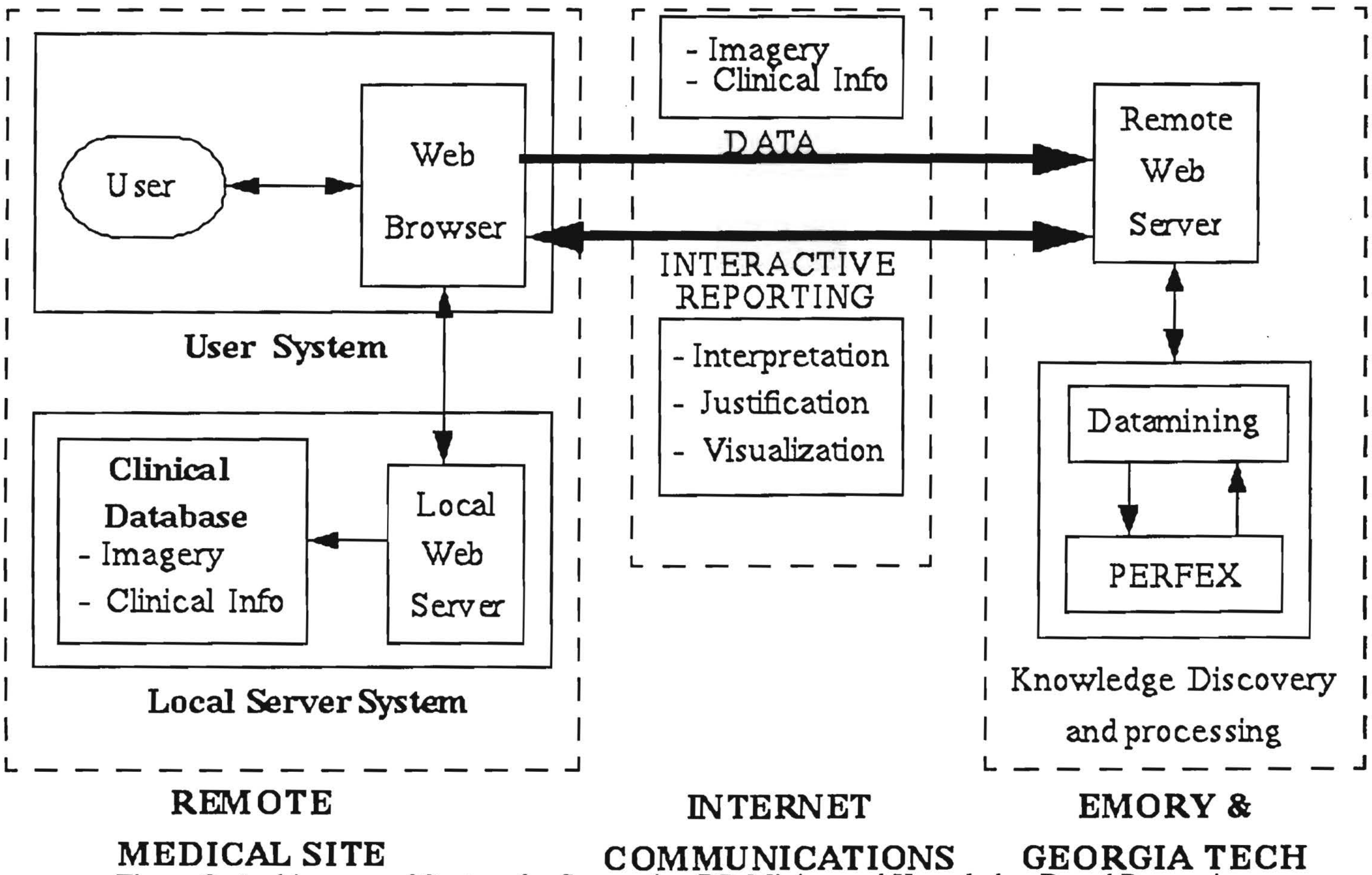

Figure 2. Architecture of System for Supporting DB Mining and Knowledge-Based Processing.

DB Design This task is devoted to the design and implementation of a DB file format that contains all the pertinent information needed by the DB mining algorithms. Initially, two general classes of DBs will be created: a <u>local</u> DB (residing at Emory University Hospital, EUH) and a <u>global</u> DB (consisting of information obtained from five different medical centers and combined with additional patient files from EUH). The five medical centers collaborating in this project are: (1) Cedars-Sinai Medical Center, LA; (2) Baptist Hospital of Miami, FL; (3) Roosevelt-St Lukes Medical Center, NY; (4) University of California at San Francisco, CA; and (5) Mid America Heart Institute' CC, Kansas City, MO. (Letters from the project co-investigators expressing their commitment to this task are included.) The ensemble of global and local files comprise the <u>distributed</u> DB.

At each of the five external sites, two separate DBs will be maintained: one with image information and the other with textual/numerical (alphanumeric, or "alfanum" for brevity) information. In both of these (image and alfanum DBs), the patient names will be encrypted to preserve patient privacy. The same file definitions and encryptions will be used for the local and global DBs. Thus, a total of four types of DBs will be created: a global and local DB, and for each of these there will be an image and an alfanum DB. The global DBs will consist of at least 1000 stress/rest myocardial perfusion SPECT studies which have been combined from all remote sites and

Emory. Five to six hundred studies will come from Emory and four to five hundreds from the five external sites.

The image information file consists of the patient's encrypted name and an identification (ID) number, the date of the study and the descriptors generated by the CEqual program for quantifying myocardial perfusion (previously described in Section C.1). This CEqual program, which is presently running in over 2,000 nuclear medicine systems world-wide, automatically generates a set of 32 descriptors to describe the location and severity of each stress-induced perfusion defect, and 32 additional descriptors to describe the location and magnitude of defect reversal (improvement) at rest (as illustrated in Figure 1). This is the same image representation scheme we have used for knowledge-based processing, as discussed earlier. The alfanum files consist of the patient's encrypted name, followed by fields related to the individual's pertinent clinical information and other demographics. Importantly, these files will include the human expert's interpretation of the perfusion scan as well as the results from coronary angiography, each of which will be used individually as gold standards for later analysis. The pertinent information will be extracted from the newly created, distributed cardiac DBs for mining. We will thus insure the integrity and security of the institutions' cardiac data banks, since all DB mining operations will be done after appropriate translation and encryption. In addition, the DBs will have a common format to facilitate the mining operations. The output of the image and alfanum files can be matched by the same encrypted names or patient IDs. The exact description of the alfanum file can be found in Appendix E.

In addition, each DB will be <u>characterized</u> in terms of patient and disease demographics including: (1) total number of patients, (2) males vs females, (3) range and mean age, (4) number with previous myocardial infarctions, (5) number of CAD vs. normal patients, (6) breakdown by number of diseased vessels, (7) breakdown by vascular territory, (8) agreement between human expert and coronary angiography in diagnosing disease. These characterizations will be generated for each site and compared both to the DBs from other sites as well as to the global data (with the site in question removed from the latter) to insure DB structure homogeneity and integrity.

During the first phase of the research, both the image and alfanum DBs from each site will be exported in its entirety to our (EUH and GIT) institutions. Hence, initially most operations will be done locally (at EUH-GIT) with the multicenter data. Once the Internet-based system is implemented, these searches and consultation sessions will be repeated remotely and compared to the local results, as discussed later. It should be observed that these tasks require a significant effort in terms of organizing the interaction with each of the sites to access and translate the data. In sites where the CEqual program has not been used on every patient, we will be responsible for processing these patients through this program. To this end, we expect to travel to the external sites as required, and have therefore requested some funds in the budget to support this travel.

Distributed Telecommunications Architecture and Middleware This task will consist of an incremental process taking place in all proposed years of research. The purpose of creating this layer of supporting middleware is two-fold: to support access to distributed DBs and to allow users to access the KB for consultations. Although both of these purposes are equally important from the research viewpoint, they are quite different from the usage and usability viewpoint. In order to aid clinicians in the diagnosis of coronary artery disease, it would be desirable to allow as many clinicians as possible to consult and interact with the KB resulting from our efforts. Thus, our "userbase" in this context should ideally be as large and diverse as possible. This is quite different to the group of intended users who will access remote DBs: this latter group, in fact, only consists of authorized members of our research team involved in data access, retrieval, and mining- by contrast, a rather minuscule userbase with very specific goals which don't generally require real-time interactions such as interactive visualization or query support. Hence, most of the efforts in this task are devoted to the much greater demands created by the larger group of users who will hopefully access the KB.

Current methods of distributing finished applications to end-users, either through the Internet or by distributing digital storage media, introduce undesired limitations for both clinicians and developers. For instance, for each future improvement made to the KB, no matter how minor, an additional distribution will have to take place. This causes undesired delays for updates to take effect at the user level, and increases in the workload for both developers and users. In addition, the userbase may still be using any older distributed version of the knowledge base. This will limit the usefulness of user experience towards further improvements in usability and accuracy of the KB. Furthermore, the use of multiple platforms by users will necessitate the creation of many separate versions for distribution. This would be a major demand of resources that could otherwise be spent on basic research issues. We thus propose a different method of providing the access to, and consultation with, PERFEX. Our solution is to maintain, upgrade and refine the KB locally, while allowing users to access the KB remotely. This has a number of significant advantages. As the use of electronic communication increases, new tools emerge rapidly which facilitate the ease in which these communications take place. These new tools can be used to address the aforementioned issues. Specifically, remote use of the KB by clinicians will eliminate any need for an elaborate upgrade cycle as improvements to the KB are being implemented. Each user will always use the latest, centrally controlled system, without the need for local time and effort-consuming changes to be made. This will also essentially eliminate the problem requiring user "retraining" with the system. All participating clinicians will be using the same, latest version of the KB seamlessly and transparently.

To solve the cross-platform portability problem, we propose to use the JAVA programming language for the implementation of the communication and user interface. As in Sections C.1 and D.2, the design of the UI will require a prototype-refinement approach. The overall system architecture is that shown in Figure 2, which allows the remote user to prepare for the interaction by accessing the local patient database through the use of a browser, which accesses a local Webserver. The Webserver is capable of accessing a local patient database, using a JAVA-based DB tool such as JDBC (JAVA DB Connectivity, which in fact will be our first choice, although the explosive nature of the field is such that better tools JDBC might soon become available and will certainly be considered). This arrangement provides full control to the local users of what information is allowed to be exchanged with PERFEX. After that, the interaction is initiated by invoking PERFEX through a password-based protocol, and subsequently providing the input data to PERFEX. The resulting output is a WWW-based page that provides secure access to the results as well as supporting query responses. (Later discussions will describe in greater detail the specific security and UI interactions.)

On the server side, PERFEX can initially be accessed through a CGI-script. To increase flexibility and facilitate the addition of more complex security methods, this will eventually be realized using server-side JAVA Applets, also known as Servlets. On the client's (clinician user's) side, the input data can initially be provided through a masked form-based system. A local Webserver can function as a gateway between the "local" (actually remote to EUH-GIT) DB and the client-user. Eventually, locally served and run JAVA code (i.e., executed at the client's remote site) could perform similar though far more complex and flexible functions through a system such as JDBC. The output shall initially be provided through a UI consisting of a hierarchy of actual WWW pages. Later on in the project, JAVA can be used to execute the UI at the client side. A separate UI program called "Perfuse" has already been implemented as a separate entity [Bra95]; it has not been ported to JAVA but will be in this program. An additional advantage of this architecture is that the computational burden is distributed among the clients. Due to these considerations, we envision an architecture implementation in JAVA and related subcomponents and tools (e.g., JDBC, Applets, and Servlets).

Security Issues Several forms of security must be addressed in the proposed project: (1) Client and Server authentication; (2) Privacy, and (3) Data integrity. Regarding client and server authentication, impostors should not be able to access either patient data or the knowledge base by pretending to be a legitimate user. Privacy considerations further require that listening in on the communication should not allow undesired third parties to obtain private patient information. And the integrity of the data should be such that no third party should be able to influence legitimate data stored on either the client or server side, nor be capable of altering the data while in transit. The above facets of security are highly common [UNRE97]. They play a vital role in commercial use of the internet (together with methods that provide accountability). Therefore, the above security issues can be easily solved by applying standard approaches currently available on the Internet. Since participation in our proposed project shall be limited and controllable, a secret-key algorithm like the public domain algorithms DES, Triple-DES (Data Encryption Standard) or IDEA will be sufficient. Public-key algorithms can be used in conjunction with that to exchange secret keys on-line, if required. Examples are RSA, for which the major USA-patents will expire by the year 2000, and Digital Signature Standard, another public domain algorithm.

The above tools are part of freely available software on the Internet, for both the server and client side. The S-HTTP (Secure HyperText Transfer Protocol) security protocol offers a large selection of cryptographic features, and is supported in several webservers like those from the NCSA (National Center for Supercomputing Applications), CERN, Spyglass and IBM, as well as the freely available and widely used Apache webserver. On the client side, it is available on WWW browsers like Mosaic, with toolkits available to add S-HTTP to other browsers. Another protocol is SSL (Secure Sockets Layer), which is supported by Netscape [NETS97] and Microsoft Internet Explorer, both freely available, and those companies' webservers. The US-only implementation uses a 128-bit key size for the RC4 (RSA) stream encryption algorithm, so the effort required to break any given exchange of information will be a formidable deterrent against brute-force decryption techniques. The server authentication uses RSA public key cryptography in conjunction with ISO X.509 digital certificates.

D.1.2 DB Mining This task continues our ongoing, preliminary efforts (Section C.3) to develop algorithms for mining DBs that combine both image and textual information. The emphasis is placed on algorithm development for finding associations, negative-rule and incremental DB mining, as well as association rules for sequence and quantitative data. As observed in Section C.3, we propose a novel approach that combines (i) data partitioning and (ii) domain knowledge along with support. The idea with data partitioning is that, once we find an association with the minimum support, we partition the data to just those records that contribute to the support for the association. The use of domain knowledge will initially be driven by the use of "rule templates" which will be used to induce rules that generally conform to the template while avoiding generating rules that do not fit the template. For example, we might look for associations/rules that involve a diagnosis as the consequent of the rule. This would be a rule template, where the consequent is fixed but the antecedent is not. The antecedent may be one or many attributes that are mined by our algorithm. In addition, the consequent in the rule template may be a subset of the mined consequent. Both of these techniques will be used to prune the search space as well as to help ensure that interesting associations/rules are discovered. This two-pronged approach will guide the implementation of the following algorithms.

Negative-Rule Mining It is important to consider the complementary problem to association finding. For instance, what fields a patient record is unlikely to show given certain findings in the perfusion image. We call these types of rules *negative association rules*. Finding negative associations is not straight forward due to the following reason: if there are a large number of items (e.g, tens of thousands) and the absence of a certain item combination is taken to mean a negative association, then we can generate millions and millions of negative association rules. Most of these rules are likely to be extremely uninteresting. The problem is therefore one of finding only *interesting* negative rules. We call such rules *strong* negative rules. It is noteworthy that there has been no reported work on mining negative rules. The development of the theory and algorithms in this area would represent pioneering work in database mining.

The measure of the degree of interestingness of a rule is defined in terms of the "unexpectedness" of the rule. This is only an objective measure of interestingness. Whether a rule is interesting or not may depend on many other factors. Simply stated, a rule is interesting if it contradicts or deviates significantly from our expectation based on previous belief. The previous belief is usually stated in terms of the a priori probabilities based on our knowledge of the problem domain. In information theoretic terms, the a priori probabilities represent our state of *ignorance* and the deviation of the a posteriori probabilities represent the degree of information gained. For an association rule $X \Rightarrow Y$, we compute its confidence as $support(X \cup Y)/support(X)$. In the absence of any prior knowledge, we can assume the items appear independently of each other. Therefore the expected confidence of the rule is $support(X) \times support(Y)/support(X)$. If the actual confidence deviates substantially from this quantity, we consider the rule to be interesting. It should be noted that usually a rule is considered useful if its confidence is relatively high, say 80%. However, if the fields appear independently then the computed confidence measure is likely to be quite small, say 1%.

These formal relationships supporting mining for negative rules are necessary due to the following reasons: (a) without these constraints, we may find millions (perhaps billions) of negative associations in the data; and (b) in the absence of such constraints, almost all of the negative associations will be extremely uninteresting. From the preceding discussion one might conclude that negative associations are inherently uninteresting, but there are many situations where this has been shown to not be true. Indeed, therein lies the power of this technique: in discovering unexpected negative associations. The basic idea behind our approach is to look at only those cases where we expect a high degree of positive association. If the actual support is found to be significantly smaller then we can conclude that they have a negative association.

Incremental DB Mining Currently, data mining algorithms work by making several passes over the entire database to find associations. If new information is added, the algorithm must be run again over the larger set of data. There are no algorithms that have been devised to reduce the amount of work to be done when additional information is added to the DB. We plan to look at incremental data mining that would avoid having to re-read all of the current data in the database. We will initially consider an approach of trading off processing time for space and hence avoiding re-reading and processing the original data. The procedure will be constrained to instances when a fixed number of new records have been added (rather than an arbitrary number of records). We feel that we can accomplish this by saving not only the large itemsets and their counts but also a set of candidate itemsets whose counts were ε-less than that needed to satisfy the minimum support.

The actual value for ε would be tied to the total number of records we plan to insert incrementally. For example, if we plan to insert 100 records incrementally into our existing database, then we will need to store the large itemsets produced by the association-finding algorithm and their counts and also those candidate itemsets whose $(count + 100) / database\_size$ would be greater than the minimum support. From that information, we believe we would only need to look at the new data and the counts we have stored for the old data. It is expected that the storage for the counts would not be excessive even for a reasonably large incremental update to the original database. However, once the specified number of new records had been inserted we would have to run the algorithm over all of the data to compute the correct counts needed for inserting additional records. So we would alternate between incremental mining and mining using the entire database. Although this technique would have to be developed and proven in our future work, it nevertheless represents and exciting and possibly valuable innovation to DB mining.

Association Rules for Quantitative Data In much of the work on data mining, association rules have been found with respect to attributes that take on a Boolean value. For example, the presence or absence of a condition, or of a clinical variable. However, much of the information is not Boolean but quantitative, especially the medical data of interest. The straightforward application of the standard Boolean mining approach, i.e., defining a Boolean attribute for each combination of the original attribute-value pairs would generate too many Boolean attributes. For example, the *age* attribute may draw its values from the domain $\{1, ..., 90\}$. This would induce 90 Boolean attributes just for this one quantitative attribute. The explosion of the number of attributes would make the algorithm unworkable. To address this issue, there has been some recent work on efficiently mining quantitative rules [FMMT96, SA96]. An example [SA96] of such an association would be the following: "10% of males between the age of 50 and 60 have at least clinical findings A and B." To deal with quantitative attributes, the values will be partitioned and adjacent partitions combined where necessary. However, the authors [SA96] also showed that a direct application of the above idea can result in too many rules. In [FMMT96], the authors examine the problem where there are 3 attributes, two numeric and one Boolean. They consider the two numeric attributes as representing a point in a two-dimensional space, and present algorithms for computing regions that represent two-dimensional association rules and for visualizing the rules. We will apply these recent algorithmic ideas to quantitative data.

Association Rules For Sequence Data The problem of mining for sequential patterns was introduced by [AS95]. This problem is an extension of the problem of discovering association rules. It was originally motivated by the need to detect patterns in the buying habits of repeat customers. A sequence is defined as an ordered set of itemsets. A sequence $<a_1 a_2 ... a_m>$ is said to be *contained in* another sequence $<b_1 b_2 ... b_n>$ if there exist integers $i_1 < i_2 < ... < i_m$ such that $a_1 \subseteq b_{i1}$, $a_2 \subseteq b_{i2}, ..., a_m \subseteq b_{im}$. For example, sequence <(1) (3 8) (5) (7 8 9)> is contained in <(1 2) (3 8) (5 7) (7 8 9)>. However, it is not contained in <(1 2) (3 8 5) (7 8 9)>. A maximal sequence is defined as a sequence which is not contained in any other sequence. A set of findings for a particular patient ordered longitudinally according to the time of clinical testing is represented by a sequence. Such a sequence is said to be *supported* by that particular patient. The *support for a sequence* is the fraction of patients who support this sequence. The problem of finding sequential patterns is to find all maximal sequences that have a certain minimum specified support in a database of patient findings.

The problem of finding sequential patterns involves finding all large itemsets. This is due to the following observation: a large sequence (a sequence having the minimum support) must contain a list of large itemsets. Therefore, as before, all large itemsets must be determined. In addition, the support for a sequence must also be determined. Finding maximal sequences from the set of large sequences is performed in an additional step. In [AS95] an algorithm to generate all sequential patterns is described. Finding sequential patterns is much more expensive than finding association rules. In the proposed research, we intend to invoke the techniques applied in improving the algorithm for finding association rules to solve the problem of finding sequential patterns efficiently. We expect gains due to the following: (a) reduction in disk I/O by applying our partitioning strategy; and (b) choosing more efficient data structures permitted by considering smaller portions of data at a time. The resulting temporally-based sequences will be evaluated to determine their medical significance, and, if found interesting or valuable from this perspective, will be subsequently reproduced to further confirm these findings.

Algorithm Efficiency In our current, preliminary efforts, we implemented a rather simple algorithm for finding associations in a relatively small set of data. Despite its simplicity, the algorithm still produced interesting results, as discussed earlier. Due to the relatively small size of this preliminary database, both the processing time and memory utilization associated with the algorithm were minimal. However, when we enlarge our DB as previously discussed, algorithm efficiency becomes increasingly important. This will be due primarily to the amount of I/O that will be necessary in processing the database records. Fortunately, we recently designed an algorithm for mining associations [SON95] that is efficient in these I/O operations. We will therefore use this technique, and continue to optimize the procedure throughout most of the research, primarily in Years 3 and 4.

D.2 AIM #2: KNOWLEDGE BASE ENRICHMENT

The goal of this project is to represent the associations, inferences and corresponding degrees of certainty discovered through the DB mining efforts in terms of rules and statistically-based relationships, such that these rules and concomitant probabilistic support can be incorporated into the current KB (PERFEX) and subsequently evaluated. The hypothesis underlying this task is that new inferences and association rules can be induced through DB mining which will result in improved knowledge-based interpretation performance.

It should be observed that this project does not actually employ "knowledge discovery" (or DB mining) algorithms, as this is done in the project associated with Aim #1 (described in the previous subsection D.1). Rather, this project deals with the representation, meaning, usefulness, significance, and relative degree of confidence associated with the associations rules and inferences resulting from the DB mining efforts. Therefore, this project is largely concerned with validating the discovered knowledge, articulating it in useful forms, and placing it in its proper medical and clinical context, and will span the entire research period.

D.2.1 Formulation Of Rules. This task consists of formulating rules in two ways: (i) through well-known knowledge-acquisition methods [Cha85, Buc84, Mus90] which have previously been used in the project [DeP89, Ezq93, Ezq96b], and (ii) through the DB mining efforts of Aim #1. The rationale for this task is based on previous clinical evaluation results, which show that the main limitation of the current KB, PERFEX, is its reduced specificity for detecting and localizing CAD. More precisely, from our case-by-case analysis, we have carefully documented that the main cause of this reduced specificity is the partial absence of non-imaging clinical variables and associated interpretive knowledge. For example, an expert knows that a patient with left bundle branch block (LBBB, a myocardial conduction abnormality) might exhibit a septal region with reduced counts due to this conduction abnormality rather than due to CAD. Thus, reduced counts in the septal wall in a patient with LBBB will be read by the human expert as a normal variant, although PERFEX will interpret this as evidence of hypoperfusion of the septal wall due to a stenosis in the left anterior descending (LAD) coronary. This is, of course, one of many possible instances in which clinical variables are required for a more comprehensive diagnosis. With this in mind, we will extend and refine the KB through these two methods.

We have identified all of the clinical variables that to date have not been incorporated into the knowledge base. There are several categories of variables that will be included: (1) effects due to patient motion, technical quality of the acquisition, attenuation because of breast/chest characteristics, location and magnitude of attenuation; (2) hypertension; (3) LBBB; (4) lung uptake; (5) transient ischemic dilatation; (6) enlargement of size and/or mass of the LV and RV; (7) LV aneurysm; (8) myocardial thickening location (wall) and magnitude; (9) ECG Q-wave results; and (10) patient symptoms. The line-by-line, itemized list of variables is given in Appendix E. To integrate this information and associated knowledge, we will undertake a systematic knowledge acquisition effort employing well known methods [Cha85, Buc84, Mus90], similarly to the techniques we have previously used extensive in constructing the KB. We will utilize rule- and frame-based knowledge representation models to extend the KB in this manner. In addition to this knowledge-acquisition effort, we will continue to use the algorithm developed in our preliminary studies to mine the DBs containing both image and clinical variables. The basic algorithm has already been described in Section C.3, while the underlying data structures, file formats, and supporting architecture were described in ection D.1. Using this algorithm and both the local, and distributed DBs, we expect to generate candidate association rules for subsequent verification and evaluation. In addition, the algorithm will be extended to address incremental and negative-rule mining as well as to generate association rules for sequence and quantitative data; these algorithmic extensions, as well as optimization issues, have also been previously described. It is worthwhile noting that we will thus be in a position -and plan- to compare "standard" knowledge-acquisition approaches with "automatic" knowledge-discovery methods.

Knowledge Confirmation In this task, we will perform two experiments: (i) search for association rules that may be present in the current KB, and (ii) specifically design the DB mining procedure to generate rules that also exist in the KB. These experiments are designed to show that the DB mining algorithms can "discover" knowledge existing in the KB (thereby serving as a means to validate the DB mining methods), as well as to confirm that the knowledge currently residing in the KB is supported by the data. The mining algorithms will be used with the global DB containing all the (local and external) sites, and also with site-specific DBs. The global DB will be valuable in documenting the validity of the rules, while analyzing the DB mining results as a function of specific sites will be useful in documenting possible differences between sites.

The knowledge confirmation studies will use the "rule templates" and the measures of confidence and support previously described. With these methods, determinations will be made regarding (i) the degree to which rules in the KB were confirmed by the DB, (ii) the degree to which the KB confirmed the DB mining algorithms, and (iii) the degree to which there were discrepancies or discoveries of new rules (where the latter will be discussed further below). It there is insufficient support for association rules, we will determine whether to delete such rules from the KB. Rules with weak support or certainty will be examined to determine whether the corresponding equivocal inferences are valid (for example, the rule "If there is breast attenuation then it is equivocal that the patient has LAD disease" is in itself a weak yet valid association). It is expected that most existing inference rules are valid and will remain. It is also expected that many of the certainty factors that were heuristically acquired will be modified resulting in more accurate interpretations. These modified rules will be made part of the permanent knowledge base only if the incorporation of this rule proves to increase accuracy and robustness.

Discovery and Assessment of New Knowledge We again recall that a matrix of algorithms and DBs will provide the information on which the efforts of this task will be based. With this matrix of possibilities in mind, we will systematically explore several strategies for validating and assess new knowledge.

(1) The first effort will take advantage of the knowledge confirmation studies discussed above, as these studies may result in rules that could disconfirm or deviate from existing rules, or which seem to be weakly supported by the data. We will examine all the rules which fall into these categories and determine the degree to which any new information has been found. We expect that this effort will probably not generate highly interesting or significantly new knowledge as much as it will suggest refinements to existing knowledge. However, we do expect that this effort will lead to a more statistically sound basis for assigning certainty values to the rules. The probabilistic issues associated with DB mining have been described in Section D.1 and are further elaborated later. Consequently the overall result derived from this effort is expected to be rule and certainty-factor refinement.

(2) A second effort may be described as discovery of "common sense" knowledge and is inspired by Martin's Law [Mar78] regarding the nature of learning, which suggests that learning (as a generalization of knowledge discovery) is profoundly affected by what is already known. In this approach, we will survey the experts (primarily the participating Emory scientists, and as many of the collaborating scientists at the five external sites as possible) for inferences that they suspect to be true and useful but which they do not use (or are

not in PERFEX currently) for lack of "hard" evidence. An example of such a rule might be: "If a patient weighs more than 300 pounds and there are fixed or slightly reversible perfusion defects in the images, then it is indeterminate whether the patient has CAD (due to significant photon attenuation and low counts)." We expect that such inferences will be induced by the mining algorithms, albeit with low levels of occurrence. However, by being able to support these associations with actual clinical data, the inferred knowledge is directly reinforced, thereby endowing the KB with this additional of "common sense" knowledge. This knowledge falls in the category of knowledge known to the experts but not to the KB. Interestingly and importantly, the problem of creating common-sense knowledge has been a key research question in knowledge-based systems research.

(3) A third method of inferring new knowledge will rely on the study of "near misses". Here we will differentiate between rules that are new to the KB and rules which are new to human experts. The approach is to first identify all patients in whom there were differences in interpretation between the knowledge-based system PERFEX and the human expert in one specific -and important- diagnostic field: identification of LAD disease. A characterization of this subset of patient cases will be made as described in Section D.1.1 (including information such as mean age, proportions of males and females, weights, and the predefined clinical variables and image information). The results of this population's characterization will be compared to the characterization of the population of patients where there were no differences in the interpretation of the same field (i.e., LAD). The variables whose values reach significant differences between these two patient populations will be isolated to infer rules. This will be done in a systematic, variable-by-variable hierarchy.

As an illustration of this experiment, consider the situation where a trend is discovered in patients for whom PERFEX concluded LAD disease to be present whereas the domain expert did not make this conclusions. This trend identifies a specific subset of cases. In this subset, a (second) trend is discovered suggesting that the hypoperfused region of the LAD vascular territory was the septum (this finding is obtained from the image DB). Then, a sub-subset of all patients with septal hypoperfusion will be created. A further trend is then found suggesting that, in cases in which PERFEX did not agree with the domain expert regarding the presence of LAD disease, all of those showing a septal defect also have left bundle-branch block (LBBB, a variable contained in the alphanumeric DB). It is then subsequently found that in patients with septal defects and LBBB, the cases of disagreement between PERFEX and the domain experts are those for which the septal defect is confined to the septum. This iterative DB mining process can suggest the following inference:

IF	the perfusion defect in the LAD territory is isolated to the septum AND the patient has LBBB AND the defect does not extend into the apical region
THEN	there is (CF) negative evidence that the patient has LAD disease.

The CF value would be determined according to the mathematical development described in our previous report (and discussed later). Note also that a second rule might also be generated when the defect extends into the apical region confirming LAD disease.

(4) A fourth method of inferring new knowledge will concentrate on the angiographic information. The rationale is that, as discussed in Section B, coronary angiography (X-rays of coronary arteries enhanced by a contrast medium and obtained via catheterization) remains the gold standard for assessing the extent and severity of atheromatous obstruction [Gou86] and therefore this information should be mined in conjunction with the information derived from perfusion imaging and clinical variables. The iterative mining techniques described above will be repeated to consider agreements between interpretations made by the KB and those made by experts but which disagreed with the angiographic results. This experiment is expected to uncover discrepancies that reflect those inherent differences between the anatomic and physiologic information that corresponds to each of these cardiac modalities. It is anticipated that some discovered rules will be considered to be new to the experts.

A fifth investigation consists of a series of experiments that will consider associations as a function of individual DBs associated with specific (external) medical sites. The reasoning is that there may be biases in the patient populations, or patterns in either the values of clinical variables, imaging information, diagnostic interpretation, or combinations of these. Once again the individual informational fields will be systematically analyzed in order of medical importance in order to determine the support and confidence of possible findings. As this experiment relies on the availability of the distributed DBs, it will be performed during the third year of the project and evaluated during the fourth year.

D.2.2 Creation of Justifications and Queries As pointed out in the progress report, a major accomplishment during the previous funded period was the incorporation of interactive justifications for the conclusions reached by PERFEX. This greatly enhances and facilitates user interaction. For instance, when the user clicks on key words in the PERFEX report shown on the screen, the system would provide the reasoning used in making those conclusions. The explanatory clauses are paragraphs written in plain English language (with proper medical terminology) stringing together sentences to explain the rules that were fired to reach the specific conclusion being questioned. Graphical illustrations of these and other UI capabilities will be discussed later.

Since of the rules will be inferred from, and confirmed with, information contained in the DBs, it will be possible to determine the support and confidence associated with the rules. We will incorporate these statistics into the interactive justification mechanism by first recording this information while also assigning appropriate pointers to these statistics in the corresponding rules. When the user clicks on a key word or field of interest, the system will respond with both the justification text and the corresponding statistics, thereby providing real-time, interactive statistical support for the justifications.

For example, if the report indicates that the patient being studied has RCA disease, then by clicking on the statement containing this "RCA-disease" conclusion, the system would respond by providing text that explains that this patient has a perfusion defect in the inferior side of the inferolateral wall which is associated with RCA disease 80% (80/100) of the time in the patient population. Thus, the user is informed that of 100 patients in the global data who had a perfusion defect isolated to the inferior side of the inferolateral wall, 80 were found to have RCA disease. And, following this action, a second, user-initiated command would provide further information on the other 20% of the cases. In this manner, we will create both the explanatory text as well as the corresponding statistics supporting interpretive conclusions. The justifications will therefore be greatly enhanced by the integration of the statistics mined from the DB.

There are other associations that will be provided with the justifications. In particular, it is possible to provide additional decision support by allowing the user to specify matches in the DB to specific cases (or to specific clinical variables in a patient case). For instance, the system may inform the user that of 100 patients with a perfusion defect in the inferior side of the inferolateral wall, there were 15 male patients, less than 40 years old, who turned out to have normal RCAs according to coronary angiography (in this case due to diaphragmatic attenuation). Clearly, this type of DB query is not trivial and may not prove to be efficient as a real-time interactive task. However, we will determine what types of DB queries and searches might be feasible both in local and distributed environments.

D.2.3 Formulation of a probabilistically based representation of uncertainty There are two aspects to this work. One relates to the integration of probabilistic reasoning models in the KB to incorporate the a priori likelihood of CAD, such that this a priori likelihood is directly taken into account by the KB when making a diagnostic interpretation. The other aspect has to do with the formulation of statistics inferred from the DB mining efforts (and which are not necessarily related to a priori likelihood of CAD). Considering the latter first, statistical measurements of certainty (statistical significance) and support (frequency of occurrence) are calculated during the DB mining process itself, thereby providing numerical values of these measures directly from the clinical data. As illustrated in the example, these statistically derived values of certainty and support will be used in the rules to replace the heuristically-derived "certainty factors" (CFs) used previously in our work [Ezq96b]. Syntactically, the form of the rule will not change (i.e., there will still be certainty values associated with antecedent and consequent clauses of the rules), but the actual values of the certainty factors will be statistically derived.

The motivation for including the a priori likelihood of CAD is that expert physicians are greatly influenced in their decision-making process by the presence or absence of symptoms such as chest pain, as well as by independent clinical findings, such as ECG S-T segment depression, hypertension, and renal dysfunction. The mathematical expressions relating a patient's symptoms and clinical findings to a pre-test likelihood of disease was developed in the foundational work of Diamond and Forrester, coupled with Bayes's Theorem [Dia79, Dia81, Dia89]. In our previous work, this probabilistic approach had been incorporated into the knowledge-based interpretation process by expressing the a priori likelihood in terms of the CF Model [Cha85, Buc84] to adhere to a symbolic knowledge representation, heuristics-based reasoning framework What we propose to do is to reverse this relationship, and represent the (current) CF in terms of a priori (or pre-test) likelihood of CAD following the formulation of [Dia79], [Dia81] and [Dia89], resulting in the post-test likelihood. The full mathematical formulation is provided in the preprint of Appendix G, which includes the graphs and curves the describe the relationships between CF values (ranging between -1 and +1) and probability (ranging between 0 and 1).

D.2.4 Evaluation Experimental Design In this task we will conduct extensive testing and evaluation of the KB with large, prospective, well-characterized populations using local data, performing multicenter trials, and undertaking usability tests. In the subsequent discussions, the terms knowledge-based system (or "system"), PERFEX, and KB are used synonymously. As observed in the Introduction, the primary hypothesis is that the proposed changes to the knowledge-based system will result in an improvement in the accuracy of the detection, localization and characterization (reversible vs. fixed defects) of coronary artery disease as interpreted from myocardial perfusion SPECT studies. In practical terms, the level of improvement would ideally result is similar performance (accuracy) between the system and the human experts. The first gold standard will be human experts' reading of hypoperfusion as it reflects CAD, such that the statistics will be performed on vascular territories rather than myocardial walls. Based on this, our biostatistical analysis will be as follows.

Primary Hypotheses Expressed in specific terms, the primary hypothesis to be tested is that a significant improvement in the accuracy of each of the following will be documented:

I. Expert system vs human experts (humans' interpretation of hypoperfusion is the gold standard for abnormality): (1) detection of CAD; (2) localization of CAD to a vascular territory in 3 territories: (a) LAD, (b) LCX, and (c) RCA (PDA); (3) characterization of CAD, for each hypoperfused vascular territory determine if the defect is: (a) reversible (consistent with ischemia) or (b) fixed (consistent with infarction).

II. Expert system vs Coronary arteriography (>50% stenosis of a vessel as gold standard): (1) detection of CAD; (2) localization of CAD to a vascular territory: (a) LAD, (b) LCX, (c) RCA (PDA).

III. Expert system vs Human Expert (Coronary arteriography, >50% stenosis of a vessel as gold standard). This will be used to test if the knowledge-based system is more accurate than the experts in the detection and localization of CAD: (1) detection of CAD; (2) localization of CAD to a vascular territory: (a) LAD, (b) LCX, (c) RCA (PDA).

Secondary Hypotheses The data that will be used to establish the improvement in accuracy for detection, localization and characterization of CAD (defined above) will also be used to establish that the increase in accuracy has resulted mostly from a net increase in specificity at a small or no loss in sensitivity. Since our previous results show that the expert system already compares well with the human expert in interpreting myocardial perfusion SPECT studies at a high sensitivity for detection and localization of CAD, it is expected that any improvement will come mostly from an increase in specificity.

I. Center-specific trends. Since the clinical patient data will not be required to have been interpreted by blinded multiple readers, we will not test inter- and intra-observer variation in the standard way. We will test, using DB mining techniques, to see if trends in how one center interprets a specific abnormality is consistent with how other centers interpret the same abnormality. Also, a separate analysis of accuracy will done as a function of the centers.

II. Distributed knowledge-based processing. The same data used to test the primary hypotheses (defined above) will be used to test whether the Internet-based knowledge-based system with remote DBs performs in the same way as it performs in the local environment. Here, any differences in interpretation results signify a potential flaw in the distributed implementation of the KB and thus will result in an analysis and correction of each flaw.

Statistical Analysis Process. The formal hypothesis testing will not begin until the DB mining using the current algorithm (i.e., without incremental mining or other modifications) is complete, and the resulting knowledge has been incorporated into the KB. The data used to improve the KB will not be used in the subsequent comparisons of the old versus new KB versions. In order to evaluate how knowledge of the clinical variables improves the accuracy of detecting, localizing, and characterizing CAD, separate comparisons of the change in accuracy rates for the new KB relative to human expert readers will be performed corresponding to the first six of the primary hypotheses described above (i.e., accuracy of both detection and localization for each hypothesis under roman numerals I, II, and II). Because the detection of disease occurs in one patient separately with and without clinical information, the improvement is tested using a McNemar's test [McN47] for paired observations.

Similarly, to assess the improvement in the knowledge-based system where the gold standard is the coronary arteriography results, matched analyses are also necessary. Separate McNemar's tests for comparing the improved KB to the previous KB, both relative to the arteriography results, will be performed for each area of detecting, localizing, and characterizing coronary artery disease. These comparisons correspond to the second set of four primary hypotheses. The final paired comparisons correspond to the last four primary hypotheses. That is, the improved expert system will be evaluated against the human experts where coronary arteriography is the gold standard. McNemar's tests will also be performed for these comparisons. Since there are sixteen primary comparisons, adjustment of the p-values will be necessary to maintain an overall type I error rate of 0.05. Bonferroni or Hochberg & Benjamini methods will be used to assure the appropriate type I error rate [Wes95].

Comparisons proposed within the secondary hypotheses will be treated as exploratory analyses. Evaluation of sensitivity and specificity between the old and the new KB and other similar comparisons will be univariately carried out using McNemar's test. Subsequent evaluation of other covariates on these measures of agreement can be modeled to assess whether confounding of these associations is present [Wil97]. The overall approach will use 100 patients from each of five external sites plus 600 patients from the Emory site. Initially all Internet-Based procedures will be tested at EUH-GIT simulating a remote site. The five nuclear cardiology sites and investigators committed to this project are: (1) Cedars-Sinai Medical Center, Los Angeles: Daniel Berman, M.D., Kenneth Van Train, M.S.; (2) Baptist Hospital of Miami: Jack Ziffer, M.D.; (3) Roosevelt-St Lukes Medical Center, New York City: E. Gordon DePuey M.D.; (4) University of California at San Francisco: Elias Botvinick, M.D.; (5) Mid America Heart Institute's CC, Kansas City: T. Bateman, M.D.

Sample Size Considerations Conservative methods from Lachin [Lac92] and Connor [Con87] are used to estimate the sample size required by this paired-sample design. Based on the evaluation of the fourteen separate primary hypotheses, we will conservatively adjust the type I error rate for any individual comparison to assure the overall type I error rate is 0.05. Setting the power equal to 0.90, 311 subjects will be required to detect the clinically meaningful improvement in localization accuracy of 15% changing from incorrect to correct and 5% changing from correct to incorrect. To achieve 90% power for improved disease detection, 414 subjects will be required for 10% changing from incorrect to correct and 3% changing from correct to incorrect. The above calculations are based on the current level of accuracy seen in the knowledge-based system evaluation [Gar96, Kra96] and realistic clinical effects upon these accuracy rates. Thus, the anticipated sample size of 600 subjects available for prospective evaluation of the improved system should provide excellent statistical power to assess all fourteen primary hypotheses even if there is as much as a 30% shortfall in subject enrollment or study completion.

D.3 AIM #3: DISTRIBUTED KNOWLEDGE DISCOVERY AND PROCESSING

The goal of this project is to extend the knowledge-based processing and knowledge-discovery methods such that (i) users can access the KB remotely and (ii) remote DBs can be accessed and mined. The datastructures, supporting architecture, and security measures described in Section D.1 will be used to conduct these efforts, with appropriate modifications as better tools emerge. In this section, we describe the methods for UI design (D.3.1), distributed mining and knowledge-based processing (D.3.2), and continued testing and evaluation (D.3.3).

D.3.1. User Interface Design for Remote Access to the KB The goal of this task is to design an intuitive UI that supports KB consultation, reporting, interactive 3D visualization, and query operations. From the perspective of the user, this UI will look much as the prototype shown in Figure 3.

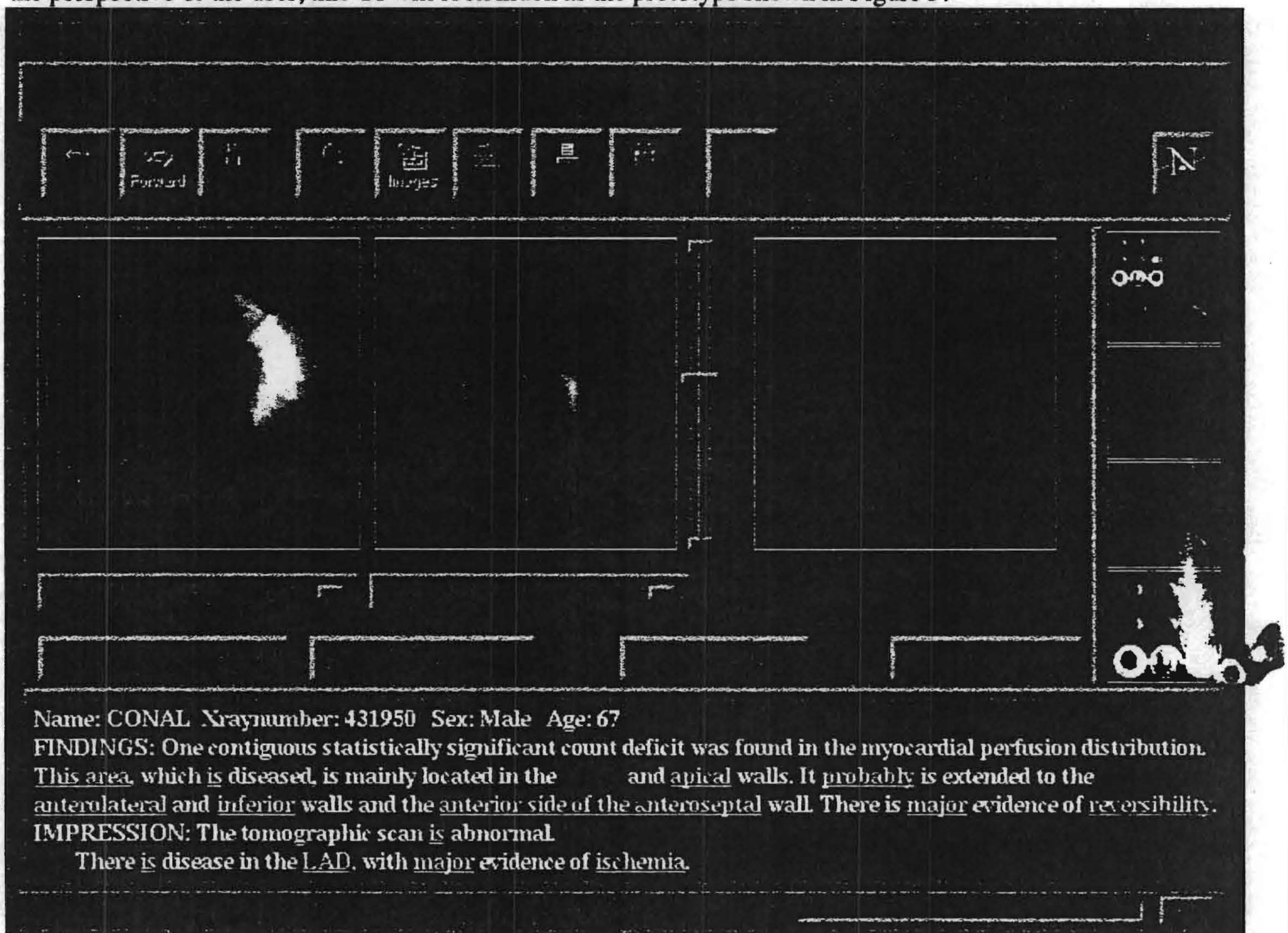

Figure 3. Prototype of the Web-Based User Interface.

This task will consist of an iterative design process which begins during the first year of research and continues into the fourth year. We will invoke basic principles and methods of HCI and UI design to accomplish this task [Bra95, Fol90, Loh90, Mar93, Shn87], as described below. Based on the subdivision of components in a UI as depicted in [Fol90], the method for properly designing a UI consists of the following phases:

(1) Problem and Requirement Analyses: These two phases are usually intended to obtain a thorough,

(1) Problem and Requirement Analyses: These two phases are usually intended to obtain a thorough, explicit understanding of the desired function of the user interface, and the tasks that should be accomplished with it. Due to the already extensive experience of the project members in this field, and the previous research done [Bra95], the only task required in this short phase is the inclusion of new tasks, that are a result of the new proposed system architecture, into the previous research results. The functions and capabilities described in Section D.2 regarding justifications, statistical support, and DB query operations, as well as other functionalities which may emerge as important, will also be defined in these phases; (2) Conceptual Design: During this phase it is determined what main concepts are part of the application. As the project progresses, additional capabilities will need to be incorporated into the design. Examples of these kinds of concepts are the inclusion of a different method of displaying information (2D versus 3D), or requiring/providing additional input/output from the user to further enhance the accuracy of the system; (3) Semantic Design: This phase is intended to make absolutely clear what the information flow is when using the application. Special attention is required here to ensure the user has all the information required to perform the desired task, without overwhelming the user with information; (4) Syntactic Design: The way in which information is exchanged between program and user is determined in this phase. Examples are the definitions of interaction styles and textual syntax; and (5) Lexical Design: During this phase the layout, colors, sizes, and all other low level information needed for a user interface design is decided upon. The initial proposed user interface will be a Web-based version of the previously developed 'Perfuse' user interface [Bra95].

(2) 3D Visualization Model Further improvements to the functionality will have a major influence on the evolution of the user interface. An important enhancement of UI will employ basic principles of graphic design such as dimensions (spacing, alignments, visual codings) to reinforce the underlying logical and semantical structures with respect to the information being presented. We will also create two types of visualizations: (i) a 3D model of the myocardial perfusion distribution that can be displayed from various perspective, and (ii) a model of vasculature, i.e., artery locations, superimposed on the 3D myocardial model, thereby resulting in a fused multimodality visualization model. The myocardial perfusion distribution model will serve to visualize hypoperfusion defects and regions of possible ischemia, while the fused myocardial-arterial model will create a 3D cardiovascular reference visualization (similar to a cardiovascular "atlas") to illustrate and support the findings. For this task, we will directly benefit from an unrelated project aimed at developing just such visualization models [Kle95, Kle92, Pei92, Coo90]. From that work, we will identify candidate myocardial perfusion distribution models as well as candidate perfusion-plus-vasculature models from a library of actual clinical cases. The look-up tables that map color to the perfusion distribution levels (as shown in Figure 1) will then be used to display the proper, patient-specific color display of the myocardial mass. A "generic" model of the vascular tree containing the major vessels (at least the LAD, LCX and RCA branches) will be superimposed on the reference perfusion distribution model to provide a graphical representation of possible anatomical and physiological interrelationships. (The user will be informed that the model sizes and shapes are not specific to the patient under consideration, but that the color-coded perfusion distribution is patient-specific.)

A further improvement is the integration of textual and graphical displays: a major improvement in usability is possible when different formats of information are correlated to each other visually. This applies to 2D versus 3D displays of SPECT imagery as well as linking textual data to its meaningful graphic counterpart. Examples are the visual feedback of the selection of a specific region of interest, such as highlighting the border of a defect in both the 2D and 3D displays, or the display of a temporary arrow between textual and graphic information, showing their interrelationships. In addition, we will also link the cardiovascular atlas to the patient-specific SPECT imagery and clinical findings.

D.3.2 Distributed Data Mining and KB Processing We envision three parts to this effort: (i) preparation of the remote sites, (ii) modification of algorithms for DB mining, and (iii) modifications (if any) of the algorithms for knowledge-based processing. The first part of this effort is confirming that all sites have or will have the necessary infrastructure architecture and software for remote access to the Web-based version of PERFEX, including an accessible cardiac data base using our previously defined structures as described and implemented under Aim#1. As remote sites access the WEB-based PERFEX for decision support, we will create a record in the global data base for both the client using the PERFEX session output and also of the data from the client's site's local DB (as prearranged with the collaborating centers). If certain key fields are missing, the record will be flagged for later review. Key fields, for example, are the human interpretation of the SPECT study and the results of coronary angiography. These two key fields may in fact be missing often during the initial consultation, since the patient might not have gone on to catheterization and probably the SPECT study was yet to be interpreted. On subsequent access by the same site on another occasion (to process other patients, for instance), the knowledge-based system will recognize all the patients flagged for missing key fields and will request these fields from the remote data base to update the global data base once the interactive consultation has ceased.

For distributive data mining, we will initially access data remotely but process the information locally. To exploit the increased amount (and possibly the semantical diversity) of the data, we will explore ways to parallelize the DB mining algorithms. Parallel database systems have been shown to be viable means of delivering the performance required in supporting very large databases [DG92]. Many commercial parallel databases are available to the users today. These are beginning to replace mainframe computers for very large database tasks. Eventually such databases may need to augment their functionality with database mining capabilities. Shared-nothing architectures have been shown to be highly suitable for parallel database systems [BBD88]. It contains a number of processing nodes each with their own primary memory and their own set of local disks. Processors communicate by message passing via a high-speed interconnection network. We will conduct our investigations (in the third and fourth years of research) by initially basing our approach on the methods given in [DG92] and [BBD88] for parallelizing our algorithms.

Regarding distributed KB processing, the basic communication paradigm was previously described in Section D.1. As noted in that section, our solution is to maintain, upgrade and refine the KB locally, while allowing users to access the KB for consultation purposes. We intend to use the JAVA programming language for the implementation of the communication and user interface. The remote user will access his/her local patient database through the use of a browser, which accesses a local Webserver using a JAVA-based DB tool such as JDBC (this in fact will be our first choice, although the explosive nature of the field is such that tools better than JDBC might soon become available and will certainly be considered). On the server side (i.e., viewed from the local perspective), PERFEX can initially be accessed through a CGI-script. To increase flexibility and facilitate the addition of more complex security-methods, this will eventually be realized using server-side JAVA Applets, also known as Servlets. On the client's (clinician user's) side, the input data can initially be provided through a masked form-based system. A local Webserver can function as a gateway between the "local" (actually remote to EUH-GIT) DB and the client-user. Eventually, locally served and run JAVA code (i.e., executed at the client's remote site) could perform similar though far more complex and flexible functions through a system such as JDBC. The output shall initially be provided through a UI consisting of a hierarchy of actual WWW pages. Later on in the project, JAVA can be used to execute the UI at the client side. Hence, we envision that eventually most, if not all, of the architecture can be implemented in JAVA and related subcomponents and tools (e.g., JDBC, Applets, and Servlets).

D.3.3. Continuation of Testing and Evaluation Efforts We envision three major considerations associated with this effort: (1) testing whether the interpretations made through remote access using the remotely accessible KB and DBs are the same as using the KB with local data bases, (2) testing whether the global data base built through the remote access process is the same as the one created by loading locally all of the patient studies from all of the sites, and (3) usability testing.

To test the accuracy of remote interpretations, we will use the formal biostatistical evaluations discussed previously in two ways. First, for each site the output files of 10 random patients used to create consultation reports will be compared on a field by field basis to those generated locally to detect any discrepancies in how the conclusions were reached. Second, a clinical validation will be performed as described in Section D.2 to determine the accuracy of detecting and localizing hypoperfusion and CAD in the same patient population. The results should be identical. If they are not, all patient output reports will be compared on a one-to-one basis between the local and remote output reports to locate the source(s) of the problem.

To test the integrity of the creation of the remotely built DB, two validations will be performed. First, once all the first 10 patients have been processed with the Web-based version of PERFEX and incorporated into the global data base, this global DB will be compared to the global data base generated under Aim#1 in Section D.1 for any discrepancies. Second, once all of the patients have been processed, the remotely built data base will be characterized (also as described in Section D.1) and its results compared to the locally built global data base. The results should show the DBs to be identical. If they are not, all patient data records will be compared one-to-one to locate the source of the discrepancies.

The iterative usability testing and evaluation cycle will consist of an ongoing process which begins in the second year of research and continues until the fourth year. Usability tests are an integral part of the UI design process, and the results of these tests are used to not only evaluate the system but also to further improve and refine it. These tests involve usage and evaluation of various versions of the knowledge-based system by users having varying degrees of expertise in interpreting myocardial perfusion studies. Criteria to evaluate the system include learning time, performance speed, user error rate, retention, and subjective satisfaction, based on well established HCI and Human Factors principles and methods [Bra95, Fol90, Loh90, Mar93, Shn87]. We have conducted extensive usability testing and evaluation efforts previously in this project as described in [Bra95]; the specific details are also presented in Section C.1. We will thus use these methods in the proposed research.

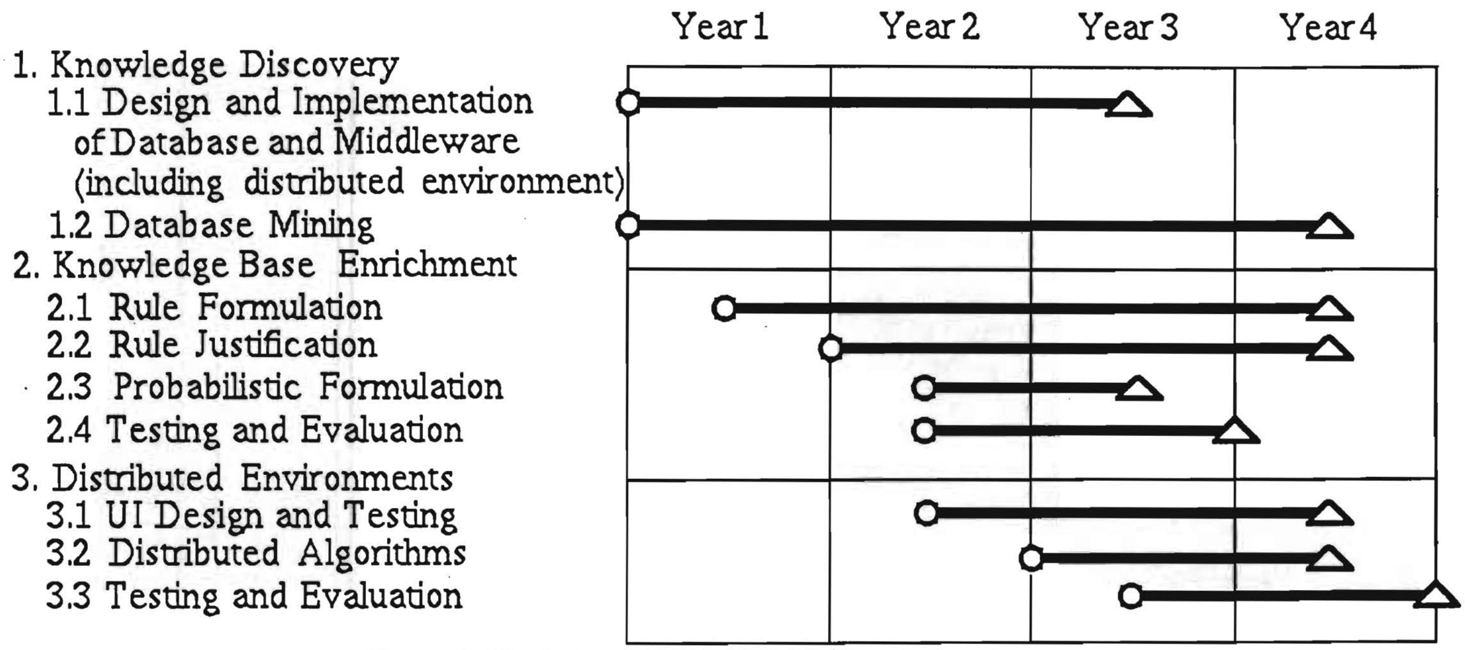

Figure 4. Workplan and schedule for the proposed project.

E. Human Subjects

This research involves previously existing data and records generated as a result of the normal clinical procedures carried out at Emory University and at the five other collaborating centers (Cedars-Sinai, Los Angeles, CA; UCSF San Francisco, CA; St. Luke's, New York, N.Y.; Cardiovascular Consultants (CC), Kansas City, MO; and Baptist Hospital, Miami, FL). No special procedures or subjects are associated with the research proposed herein. Throughout the proposed research period, patient confidentiality will be observed at theses centers, according to normal clinical practices of confidentiality filing and recording data and records, and at Georgia Tech, by supplanting names or any other indicators of identity with coded alphanumeric file headers. Also, special security encryption will be used for transmission, as described in Section D.

F. Vertebrate Animals

No vertebrate animals are used in this research in any form.

G. Literature Cited

See next page.

H. Consortium/Contractual Arrangements

Emory University Hospital will participate in this program as a subcontractor. In particular, the key personnel from Emory University listed in page 2 (Garcia, Cooke, Krawczynska, Clark, Folks) hold permanent appointments in the Division of Nuclear Medicine, Department of Radiology. These individuals will contribute as explained in the budget justification portion, which explaines their contributions primarily in the retrieval and provision of clinical data, and providing medical and clinical support in all phases of the research. The research, of course, is primarily of a medical informatics nature, but it is believed that participation of medical scientists and physicians is important in this research. The team members from both institutions have engaged in collaborative efforts for several years (as shown in the publications in Section C), and the person who will serve as PI for the Emory portion is Dr. Garcia. A letter on behalf of Emory University is attached. Dr. Garcia will be responsible for all technical and financial duties at Emory University. It should be pointed out that this is precisely the same arrangement that was successfully followed during the previous grant period.

I. Consultants/Collaborators

The consultants in this project are Dr. Berman and Mr. Van Train from Cedars-Sinai Medical Center in Los Angeles CA; Dr. Ziffer from Baptist Hospital of Miami; Dr. DePuey of St. Luke's Medical Center in New York; Dr. E. Botvinick from UCSF, San Francisco; and Dr. T. Bateman of CC, Kansas City. Their role will be to serve as participants in distributed DB mining and processing, as well as external evaluators of the system. Dr. Berman and Mr. Van Train have previously collaborated with the project investigators. They will provide their consultant services at no cost to the project.

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